CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206302Orig1s000

MEDICAL REVIEW(S)

FDA Clinical and Statistical Review of Forest Research Institute's Resubmission of NDA 206302

Application: NDA 206302
Drug: Byvalson, Combination of nebivolol/valsartan
Applicant: Forest Research Institute, a subsidiary of Forest Laboratories
Proposed indication: treatment of hypertension

Received Date: 29 September 2015
Original PDUFA Goal Date: 29 March 2016 (clock subsequently extended for major amendment)

Statistical Reviewer: George Kordzakhia, Ph.D.
Clinical Reviewer: Shen Xiao, MD., Ph.D.

Background: On February 23, 2014, Forest Laboratories submitted NDA 206302 for Byvalson (nebivolol/valsartan fixed dose combination tablets of 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg) for the treatment of hypertension in adults. On December 24, 2014, the FDA issued a complete response (CR) letter. In the CR letter, the Agency stated that "Based upon the principle that, absent a safety advantage, all components of a combination product ought to contribute meaningfully to the antihypertensive effect achievable with the individual agents (or to combinations of fewer agents), we concluded that Byvalson's effect was too small and a safety advantage had not been demonstrated." The letter further noted that the Agency had explored with the Applicant the possibility that there were more responders than one might have expected on the basis of the observed mean treatment effect, but that the Agency had concluded there was no evidence of a responder subpopulation with a more exaggerated treatment effect.

In the CR letter, the Agency proposed two potential paths forward. The Applicant could address the deficiency cited in the CR letter by providing a more compelling case for improvement in safety or tolerability of Byvalson compared with high dose nebivolol. Alternatively, the Applicant could pursue a new path to approval that the Agency was considering for fixed-dose combination anti- hypertensive therapy. The CR letter noted that "many physicians practice and guidelines promote use of lower-dose combination antihypertensive therapy on the basis that half or more of the treatment effect is manifest at the low dose, and, where the mechanisms are sufficiently distinct, one ought to expect more-or-less additive effects on blood pressure and avoidance of dose-related adverse reactions of either drug." The letter further noted that although the Agency had not to date based an approval on such a principle, it was willing to consider one, even absent demonstration of better tolerability. The Agency recommended that the Applicant abstract from the development program a characterization of the effects of the combination compared with effects of the corresponding components at the same dose and compare the results with similar information on approved combination antihypertensives, to the extent such data were available in drug labels or the literature. The Agency explained that the "goal would be to show that Byvalson doses are about as additive as are other combinations one might expect to be more mechanistically independent."

In June 2015, Forrest Research Institute met with the Agency to discuss the proposed data package and findings that would be used to support the approval of the nebivolol/valsartan FDC. Based on the discussion at the meeting, the Applicant re-submitted NDA 206302 on September 25, 2015 for the approval of a single strength of Byvalson ((b) (4) nebivolol/valsartan) for the treatment of hypertension in adults. During a teleconference on February 9, 2016, the Agency voiced concern that

the Applicant had not provided sufficient rationale for selecting the (b) (4) dose of nebivolol as the single dose for approval and questioned whether the 5/80 mg dose should be approved instead. On February 23, 2016, the Applicant submitted a response document summarizing their rationale for selecting the (b) (4) dose for approval.

This review discusses the efficacy, safety and tolerability data supporting the initially proposed dose (b) (4) (b) (4) as well as the data supporting the 5/80 mg dose.

Proposed Indication: The indication proposed in the Applicant's complete response is as follows: "BYVALSON is (b) (4) indicated for the treatment of hypertension, to lower blood pressure…." Proposed indications and usages include:

(b) (4)

Contents of Resubmission and Review Strategy: The resubmission contains a Clinical Overview, a separate document containing additional tables and figures, CMC information, and proposed labeling. The FDA clinical and statistical review focused on the analyses and information provided in the resubmission, and subsequent amendments pertaining to FDA information requests during the review. FDA's prior reviews for NDA 206302, including clinical reviews dated August 7 and December 5, 2014 and statistical reviews dated August 1 and September 18, 2015, were also referenced as needed.

Reviewer Note: Data supporting efficacy are provided by Study NAC-MD-01, an 8-week randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study of nebivolol and valsartan given either in combination as an FDC or as monotherapy in patients with Stage 1 or Stage 2 hypertension. During the first 4 weeks of the double-blind treatment period, FDC doses of 5/80 mg, 5/160 mg, and 10/160 mg were evaluated. After 4 weeks, the dose in each treatment arm was doubled; hence efficacy and safety data are available at week 8 for FDC doses of 10/160 mg, 10/320 mg, and 20/320 mg and at week 4 for FDC doses of 5/80 mg, 5/160 mg and 10/160 mg.

(b) (4)

Efficacy Findings for Nebivolol/Valsartan FDC 5/80 mg (b) (4) at Week 4

Least squares (LS) Mean Change in Blood Pressure

Table 2 shows the LS mean change from baseline in blood pressure at week 4 in Study NAC-MD-01 for FDC 5/160, FDC 10/160, placebo, nebivolol 5 mg, nebivolol 20 mg, valsartan 80 mg and valsartan 160 mg. In comparison to nebivolol 5 mg and valsartan 80 mg administered as monotherapies, (b) (4) produced statistically significantly greater reductions in SBP and DBP at week 4. The point estimate of the treatment effect of FDC 5/80 mg (b) (4) on DBP and SBP was at least 2 mm Hg greater than the point estimate of the treatment effect of nebivolol 5 mg and valsartan 80 mg monotherapies on DBP and SBP. (b) (4)

Table 2: Summary of Efficacy Findings for FDC 5/80 mg (b) (4) mg at Week 4

Treatment Group(s)	DBP (Primary)	SBP (Key Secondary)
	LS Mean Change from Baseline (SE)	
Placebo	-6.4 (0.5)	-6.5 (0.9)
Nebivolol 5 mg	-10.8 (0.4)	-11.2 (0.6)
Nebivolol 20 mg	-13.8 (0.4)	-13.8 (0.6)
Valsartan 80 mg	-10.2 (0.4)	-11.9 (0.6)
Valsartan 160 mg	-10.9 (0.4)	-13.9 (0.6)
FDC 5/80 mg	-13.5 (0.4)	-14.8 (0.6)
(b) (4)		
	LS Mean Treatment Difference (SE)	
FDC 5/80 mg vs Neb. 5 mg	-2.7 (0.5) p-value<0.0001	-3.6 (0.8) p-value<0.0001
FDC 5/80 mg vs Neb 20 mg	0.3 (0.6) p-value=0.573	-0.9 (0.8) p-value=0.287
(b) (4)		
FDC 5/80 mg vs Val 80 mg	-3.3 (0.5) p-value<0.0001	-2.9 (0.9) p-value=0.0007
FDC 5/80 mg vs Val 160 mg	-2.6 (0.5) p-value<0.0001	-0.8 (0.8) p-value=0.332
(b) (4)		

CI = confidence interval; LS=Least Square; SE=Standard Error; FDC = fixed-dose combination; Neb = nebivolol; Val = valsartan.
Source: Table 11.4.1.2.2.1-1 and Table 14.4.1.2.2.1-2. of Clinical Study NAC-MD-01 Report (pages 128 and 129) and Reviewer's Results

Additivity

To evaluate the additive effect of FDC 5/80 mg (b) (4) the Applicant calculated (1) the additivity ratio (BP reduction observed with the FDC divided by the sum of the BP reductions of the FDC's components) and (2) the additivity difference (the subtractive difference between the BP reduction from the FDC and the sum of the BP reductions of the FDC's components). Values less than one for the additivity ratio correspond to partial additivity; values equal to one and greater than one correspond to complete additivity and super-additivity or synergy, respectively. Negative values for the additivity difference indicate partial additivity, a value of 0 indicates complete additivity, and positive values indicate synergy.

(b) (4) See Table 3. For DBP, FDC 5/80 mg showed an additivity ratio of 86.6% and additivity difference of -1.1 mm Hg, again, indicating partial additivity. Partial additivity was also observed for SBP (additivity ratio of 82.2% and additivity difference of -1.8 mm Hg).

Contribution of Monotherapy Components to the Effect of (b) (4) FDC 5/80 mg

The contribution of each monotherapy component to the effect of each FDC was calculated by assessing the ratio of BP reduction observed with each monotherapy divided by the BP reduction observed with

the corresponding FDC. The resultant ratio represents the percent contribution of each monotherapy to the FDC. A high contribution ratio (i.e. ratio close to 1) for either monotherapy would indicate that the treatment effects of the respective monotherapy and the FDC are similar. The contribution ratios of the monotherapy components to the effect of (b) (4) FDC 5/80 mg (at week 4) are shown in Table 3.

(b) (4)

For FDC 5/80 mg, the observed percent contribution of valsartan 80 mg was 54% for DBP and 65% for SBP, while the observed percent contribution of nebivolol 5 mg was 62% for DBP and 57% for SBP

Additivity results for recently approved FDCs

As recommended in the CR letter, the Applicant compared the additivity findings for FDC (b) (4) with the findings for other approved combination antihypertensives. For the purpose of this analysis, the Applicant focused on recently approved FDCs, including Exforge (valsartan/amlodipine), Tekturna HCT (aliskiren/hydrochlorothiazide), Tekamlo (aliskiren/amlodipine), Valturna (aliskiren/valsartan), and Twynsta (telmisartan/amlodipine).

For reference, the additivity ratios and additivity differences of recently approved FDCs are provided in Table 10 in the Appendix of this review. As measured by DBP, the additivity ratios ranged from 72% to 129% with a mean of 83.7%; the additivity differences varied from -4.8 to 1.6 with a mean of -1.2. For SBP, the additivity ratios were between 72% and 107% with a mean of 82.5%. The additivity differences ranged from -8.1 to 0.9 with a mean of -2.6. As shown in the table below, the additivity of (b) (4) FDC 5/80 (assessed at week 4) fall within the range of the additivities of recently approved FDCs.

(b) (4)

Table 3: Additivity and Contribution of Monotherapy Components for [redacted] FDC 5/80 at Week 4

Treatment Group(s)	DBP (Primary)		SBP (Key Secondary)	
	Additivity			
	Ratio (95% CI)	Difference (95% CI)	Ratio (95% CI)	Difference (95% CI)
[redacted]				
FDC 5/80 mg (Week 4)	0.866 (0.71, 1.06)	-1.1 (-2.77, 0.57)	0.822 (0.64, 1.06)	-1.8 (-4.49, 0.89)
Mean of Approved FDC's	0.837	-1.2	0.825	-2.6
Range of Approved FDC's	0.72 to 1.29	-4.8 to 1.6	0.72 to 1.07	-8.1 to 0.9
	Percent Contribution (95% CI)			
[redacted]				
FDC 5/80 mg	62.0%	53.5%	56.6%	65.1%
Range of Approved FDC's	24.4% to78.4%		22.7% to 86.9%	

CI = confidence interval; LS=Least Square; SE=Standard Error; FDC = fixed-dose combination; Neb = nebivolol; Val = valsartan.
Source: Table 14.4.1.1. and Table 14.4.2.1. of Applicant's Clinical Study NAC-MD-01 Report (pages 985 and 987), Table 2.3.5.1–1, Table 2.3.5.2–1, Table 2.3.5.4–1.of Applicant's Clinical Overview (pages 19, 21, and 28)

Summary of Additivity Results at Week 8 and Week 4 for the Various FDC Doses

The additivity difference and additivity ratio were also calculated for nebivolol/valsartan FDC [redacted] The results of these analyses, [redacted] are shown in Table 4 below. Among the doses considered at Week 8 and at Week 4, the lower doses tended to have greater additivity ratios and more favorable additivity differences.

Table 4: Summary of Additivity for Nebivolol/Valsartan FDC at Week 8 and Week 4

Treatment Group(s)	DBP (Primary)		SBP (Key Secondary)	
	Additivity			
	Ratio	Difference (mm Hg)	Ratio	Difference (mm Hg)
Week 8				
FDC 10/160 mg	0.832	-1.6	0.810	-2.3
FDC 10/320 mg	0.800	-2.0	0.754	-3.2
FDC 20/320 mg	0.735	-3.1	0.717	-3.9
Week 4*				
FDC 5/80 mg	0.866	-1.1	0.822	-1.8
FDC 5/160 mg	0.831	-1.5	0.727	-3.3

CI = confidence interval; LS=Least Square; SE=Standard Error; FDC = fixed-dose combination
Source: Table 1.1.1.1, Table 1.1.1.2, Table 1.1.2.1, Table 1.1.2.2 of Applicant's Tables and Figures for Additivity Analyses (pages 5, 6, 14 and 15).
*Additivity Ratios and Differences cannot be calculated for FDC 10/160 mg at Week 4 because there was no nebivolol 10 mg arm at Week 4.

Rationale for dose selection

On February 23, 2016, the Applicant submitted a response document summarizing their rationale for selecting the (b) (4) dose of nebivolol rather than the 5/80 mg dose as the sole dose for approval. (b) (4)

(b) (4)

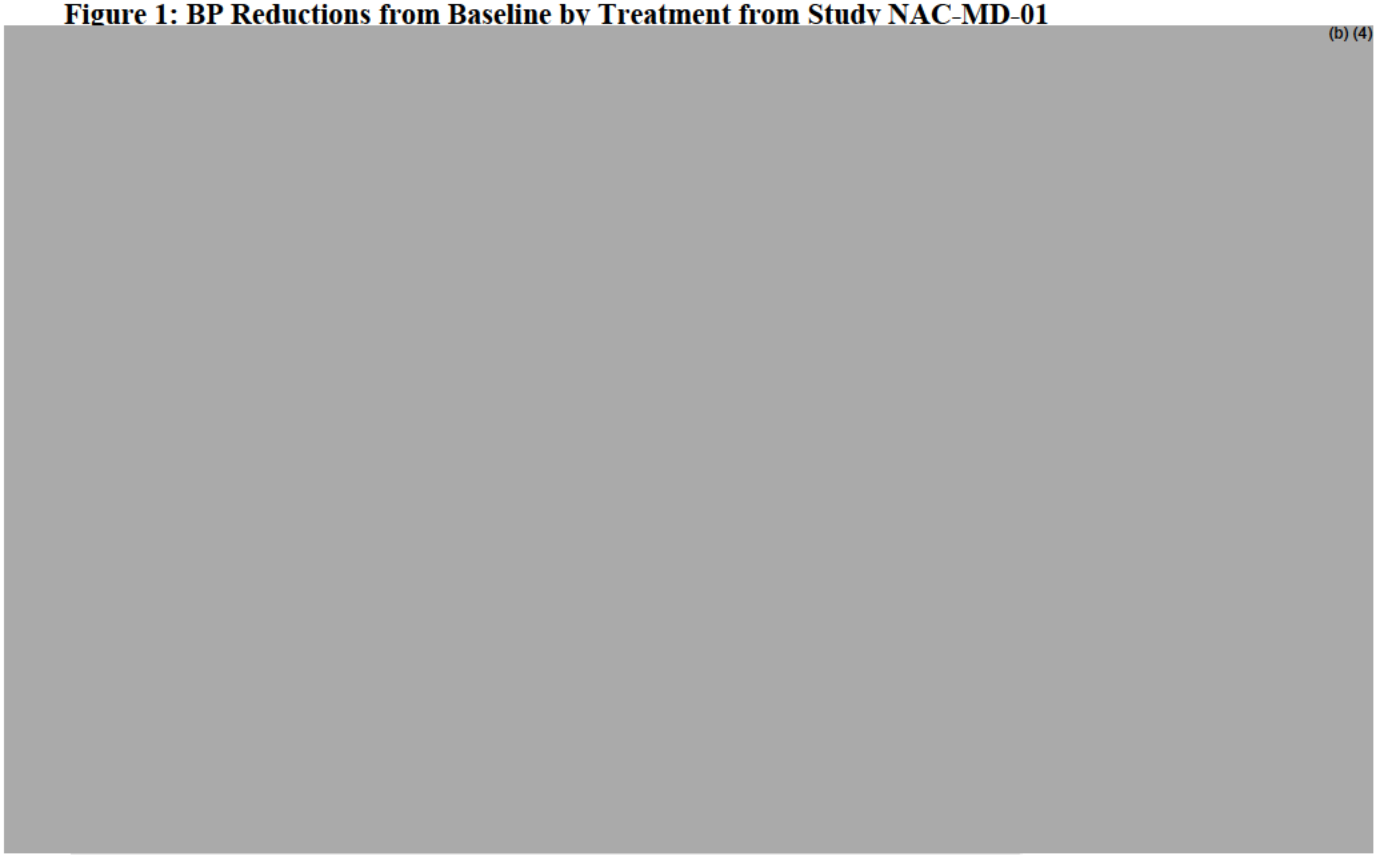
With regard to safety and tolerability, the Applicant noted that there were no discernable differences in the safety and tolerability profile of the two doses and cite analyses in support of this conclusion.

Reviewer's comment: As previously noted, during the first 4 weeks of the double-blind treatment period, FDC doses of 5/80 mg, 5/160 mg, and 10/160 mg were evaluated. After 4 weeks, the dose in each treatment arm was doubled, hence efficacy and safety data are available at week 8 for FDC doses of 10/160 mg, 10/320 mg, and 20/320 mg. The Applicant's February 23, 2016 submission included comparisons (b) (4) *with the 5/80 mg dose at week 4. These analyses* (b) (4) *are difficult to interpret* (b) (4)

(b) (4) FDA's analyses, shown below, focus on the comparison at week 4 for the reasons cited above.[1] These analyses, which include analyses of the LS mean reduction from baseline in blood pressure, the cumulative distribution of the change from baseline in blood pressure, and the probability of achieving blood pressure targets by baseline blood pressure, indicate (b) (4) 5/80 mg doses (b) (4) efficacy in lowering blood pressure.

[1] CDF plots produced by Dr. Martina Sahre, the clinical pharmacology reviewer ; probability curves produced by the statistical reviewer

Figure 1: BP Reductions from Baseline by Treatment from Study NAC-MD-01



Source: Figure 2, Forest Research Institute's Efficacy Information Amendment dated February 23, 2016

Figure 2: Cumulative Distribution of the Change from Baseline in SBP at Week 4, ITT Analysis using LOCF

Figure 3: Cumulative Distribution of the Change from Baseline in DBP at Week 4, ITT Analysis using LOCF

Figure 4: Cumulative Distribution of the Change from Baseline in SBP at Week 4, Observed Cases Analysis

Figure 5: Cumulative Distribution of the Change from Baseline in DBP at Week 4, Observed Cases Analysis

Figure 6: Probability of Achieving Systolic Blood Pressure Goal <140 mmHg at Week 4

Safety and Tolerability

The Clinical Review dated August 7, 2014 contains a comprehensive discussion of the safety findings in the nebivolol/valsartan FDC development program. As noted in that review, a total of 1664 patients with hypertension were exposed to the nebivolol/valsartan FDC for 8 weeks in Study NAC-MD-01, while a total of 807 patients were exposed to a nebivolol/valsartan free-tablet combination for up to 52 weeks in Study NAC-MD-02. Analyses of the data from these trials, as well as other trials conducted as part of the development program, did not identify any safety issues that would preclude approval. Notably, analyses of the safety data did not reveal any new or unexpected AEs (i.e., AEs that were not previously known to be associated with the FDC's components). As also discussed in the clinical review, analyses of adverse events and laboratory findings of interest (i.e., findings associated with the FDC's components such as hyperkalemia, impaired renal function and bradycardia) did not suggest a greater risk of these events/complications in the FDC groups as compared to their respective monotherapy groups.

(b) (4)

Key safety findings for FDC 5/80 are shown in table 5. The incidence of SAEs, AEs leading to discontinuation, and TEAEs (b) (4) in the FDC 5/80, nebivolol 5 mg and valsartan 80 mg treatment arms. The incidence of bradycardia was low in all treatment arms.

Table 6: SAEs, AEs Leading to Discontinuation, and Severe TEAEs – Safety Population (Weeks 0-4)

	Placebo N = 277 n (%)	FDC 5/80 N = 555 n (%)	Neb 5 mg N = 555 n (%)	Val 80 mg N = 555 n (%)
SAE	4 (1.4)	1 (0.2)	1 (0.2)	1 (0.2)
AEs leading to discontinuation	9 (3.2)	11 (2.0)	6 (1.1)	5 (0.9)
TEAEs	59 (21.3)	116 (20.9)	116 (20.9)	105 (18.9)
Sinus Bradycardia	2 (0.7)	0	0	1 (0.2)
Bradycardia	0	3 (0.5)	3 (0.5)	0

Source: Applicant's Table s 5 and 7 (pages 23 and 24 of resubmission-efficacy amendment submitted February 23, 2016); results confirmed by FDA

(b) (4)

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(b) (4)

Review Team's Conclusions: (b) (4)

From a safety and tolerability perspective, treatment with (b) (4) FDC 5/80 mg appeared to be well- tolerated. Analyses did not reveal any new AEs or AEs that would be considered unexpected given the experience with the FDC's components. (b) (4)

Recommendation on Approval: Based on the efficacy and safety findings, the 5/80 mg dose of nebivolol/valsartan should be approved for the treatment of hypertension in adults.

Labeling: The Applicant recently submitted revised labeling for the 5/80 mg dose (b) (4) ; review of the revised label is ongoing.

Appendix:

Table 10. Additivity Results for Recently Approved FDCs and Low- and Mid-Dose Neb/Val FDCs

FDC	*Dose*	*DBP*		*SBP*	
		Additivity Ratio	*Additivity Difference*	*Additivity Ratio*	*Additivity Difference*
Exforge	Val 160/Amlo 5 mg	82.7%	–1.6	76.6%	–3.9
	Val 160/Amlo 10 mg	77.7%	–2.6	80.5%	–3.6
	Val 320/Amlo 5 mg	80.9%	–2.2	92.6%	–1.3
	Val 320/Amlo 10 mg	86.6%	–1.5	85.1%	–2.7
Tekturna HCT	Alis 150/HCTZ 12.5 mg	95.8%	–0.2	90.4%	–1.1
	Alis 150/HCTZ 25 mg	128.5%	1.3	103.5%	0.4
	Alis 300/HCTZ 12.5 mg	103.5%	0.2	83.9%	–2.4
	Alis 300/HCTZ 25 mg	127.0%	1.6	91.1%	–1.3
Tekamlo	Alis 150/Amlo 5 mg	104.1%	0.3	107.3%	0.9
	Alis 150/Amlo 10 mg	97.3%	–0.3	94.2%	–1.1
	Alis 300/Amlo 5 mg	91.9%	–0.9	85.3%	–2.6
	Alis 300/Amlo 10 mg	83.4%	–2.2	71.8%	–6.4
Valturna	Alis 150/Val 160 mg	88.5%	–0.7	90.9%	–1.0
	Alis 300/Val 320 mg	76.6%	–2.5	76.2%	–4.0
Twynsta	Telm 40/Amlo 5 mg	71.5%	–4.1	77.2%	–5.7
	Telm 40/Amlo 10 mg	77.3%	–4.1	73.3%	–8.1
	Telm 80/Amlo 5 mg	80.0%	–3.0	79.4%	–5.1
	Telm 80/Amlo 10 mg	74.3%	–4.8	79.7%	–6.1
Range for Approved FDCs		**72% to 129%**	**–4.8 to 1.6**	**72% to 107%**	**–8.1 to 0.9**
Mean of Approved FDCs		**83.7%**	**–1.2**	**82.5%**	**–2.6**
Neb/Val FDC	Neb 10/Val 320 mg	80.0%	–2.0	75.4%	–3.2
	Neb 10/Val 160 mg	83.2%	–1.6	81.0%	–2.3
	Neb 5/Val 160 mg	83.1%	–1.5	72.7%	–3.3
	Neb 5/Val 80 mg	86.6%	–1.1	82.2%	–1.8

The weighted mean is calculated from all approved doses of 5 recently approved FDCs using a fixed-effect meta-analysis approach, weighted average of all measure, $W_i = 1 / \text{Var}(\text{measure}_i)$, and variance of mean of approved is 1 / sum of all W_i.

Note: Data from approved products were obtained from the Summary Basis for Approval on the FDA website.

Additivity Ratio: The ratio between the placebo-adjusted reduction from baseline for FDC and the sum of individual, placebo-adjusted reductions from baseline for each monotherapy. Additivity ratio is displayed as a percentage.

Additivity Difference (measured in mm Hg): The subtractive difference between the placebo-adjusted reduction from baseline for FDC and the sum of individual, placebo-adjusted reductions from baseline for each monotherapy.

Alis = aliskiren; Amlo = amlodipine; DBP = diastolic blood pressure; HCT/HCTZ = hydrochlorothiazide; SBP = systolic blood pressure; Telm = telmisartan; Val = valsartan.

Source: Table 2.3.5.2–1 of Applicant's Clinical Overview (page 21)

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/s/

SHEN XIAO
04/04/2016

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04/05/2016

ALIZA M THOMPSON
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04/05/2016

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 206302 Nebivolol/valsartan (BYVALSON) for hypertension.

Sponsor: Forest Laboratories

Review date: 23 December 2014

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 206302

This memo conveys the Division's decision to issue a "Complete Response" letter for this application.

This application has been the subject of reviews of CMC (Kambhampati; 24 October 2014), biopharmaceutics (Mahayni; 24 October 2014; 14 December 2014), clinical pharmacology (Sahre, Abu Asal; 4 August 2014 and 15 August 2014), clinical effectiveness and safety (Xiao; 7 August 2014 and 5 December 2014) and statistics (Kordzakhia; 1 August 2014 and 18 September 2014).

There is also a CDTL memo (Madabushi; 17 December 2014), with which I am in substantial agreement. As he documents, the only approval issue is the effect size.

Both the angiotensin receptor blocker valsartan and the beta-blocker nebivolol are approved as single agents for hypertension and have well-established safety profiles.

Approval of combination products requires each component contribute to the claimed effects (21CFR 300.50). Historically, combination antihypertensive agents have been approved based on the principle that one should obtain maximal benefit from a single agent before incurring the "dose-independent" adverse events associated with a second agent, and we have consequently required that the second agent show an effect above what could be obtained with maximum approved doses of the single agents. How large the contribution needed to be has not previously arisen, but the contribution in other approved antihypertensive combination products is on the order of 4-5 mmHg.

Labeling used to say "titrate, then substitute". More recently, where starting two agents together was well-tolerated and the target population was "far" from treatment goals, we have granted first-line indications to combination products that well characterized—and improved—the likelihood of getting to goals, depending on baseline blood pressure.

Another relevant principle has been that the steps available in a product line be large enough that it would make sense sometimes to try them rather than moving directly to yet-higher doses or to another drug. This has been applied to combinations as well, usually resulting in low-dose combination doses that were not superior to high-dose monotherapy.

We have also recognized advantages of low-dose combinations to avoid dose-related adverse events. The best example of this is Ziac, the combination of hydrochlorothiazide and bisoprolol, low doses of which provide improved tolerability compared to corresponding doses of each individual drug.

Beta-blockers and ARBs both inhibit the renin-angiotensin system, so little additivity was expected, which is why the sponsor's factorial trial, with over 500 subjects per active treatment arm, was only just able to detect an effect of the combination over high-dose nebivolol (p=0.04). An Advisory Committee agreed with the review team's and

Division's position that the demonstrated effect, judged by the principles described above, did not meet standards for approval. However, the sponsor had argued that there were subjects in the factorial trial who got effects substantially larger than the mean, so some additional work was done to explore whether there were more outlier responders than one might expect from a shift of the mean in the distribution of responses. The review team concludes that there is no evidence for such an outlier group, and I agree.

The sponsor provided some evidence that the combination was better tolerated than was high-dose nebivolol, but the review team, the Advisory Committee, and I did not find their argument persuasive. Had it been persuasive, this would have been an adequate basis for approval of the combination, although the case would not be as compelling as it was for Ziac, where the blood pressure advantages of the combination were clear, too.

The Division is currently giving consideration to an alternative principle for approval of combination antihypertensive drugs, one that, whether or not it is supported by data, appears to be in fairly common practice. The principle would be that it may be more important to avoid dose-related adverse effects than to avoid dose-independent ones. This would lead one to use low doses of several drugs, even if one might get similar blood pressure reductions with larger doses of fewer drugs. If one were to adopt this principle, then it might suffice to show reasonable contributions of the components *at the doses proposed* rather than at maximum doses.

Dr. Madabushi suggests that if one were to embrace this alternative principle to approval of combination products, the combined pharmacological classes ought to "make sense", i.e., work through different mechanisms. This is a test that neither of us believes is passed with Byvalson.

Operationally, it will be necessary to define a less arbitrary basis for deciding which low-dose combinations make sense, even if one is ready to approve combinations without having the safety advantages demonstrated. We generally approve monotherapy doses beginning with one that is about half-way up (or more) the dose-response curve. With independent mechanisms, one might then expect a more nearly additive effect of the components than there would be if the mechanisms overlapped. The extent to which this is true ought to be examined across the myriad of antihypertensive combination products before setting standards for approval of low-dose combinations of unproven safety advantage.

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/s/

NORMAN L STOCKBRIDGE
12/23/2014

Cross-Discipline Team Leader Review

Date	December 17, 2014
From	Rajanikanth Madabushi, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	206302
Type	505(b)(2)
Applicant	Forest Laboratories, Inc.
Date of Submission	February 24, 2014
PDUFA Goal Date	December 24, 2014
Proprietary Name / Established (USAN) names	BYVALSON™ (nebivolol/valsartan)
Dosage forms / Strength	Immediate Release Tablets - 5 mg/80 mg; 5 mg/160 mg; 10 mg/160 mg; 10 mg/320 mg; and 20 mg/320 mg of nebivolol and valsartan, respectively per tablet
Proposed Indication(s)	Hypertension
Recommended:	**Complete Response**

This secondary review is based, on the primary reviews of:

- OSI (Sharon Gershon), 09/05/2014
- DMEPA (Jean Olumba), 03/20/2014, 08/12/2014
- Chemistry (Rao Khambampati), 10/24/2014
- Microbiology (Erika Pfeiler), 05/28/2014
- Biopharmaceutics (Houda Mahayni) 10/24/2014, 12/14/2014
- Pharmacology/Toxicology (Phillip Gatti), 03/21/2014
- Clinical Pharmacology (Bilal AbuAsal), 08/15/2014
- Biometrics (George Kordzakhia), 08/01/2014, 09/18/2014
- Clinical (Shen Xiao), 08/07/2014, 12/05/2014

Cross Discipline Team Leader Review Template

1. Introduction

In the current submission (NDA 206302), Forest Laboratories Inc., is seeking authorization to market Byvalson®, a combination product of nebivolol and valsartan, for the treatment of hypertension, pursuant to the requirements of section 505(5)(2) of the Federal Food, Drug and Cosmetics Act, 21 CFR 314. Nebivolol (Bystolic®) was approved in the US in 2007 for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents. Valsartan (Diovan®) was first approved in the US for the treatment of hypertension as monotherapy or as a combination with other antihypertensive agents in 1996. It has also been approved for treatment of stable NYHA class II or III heart failure and for the reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

The primary basis in support of this new drug application comes from a single multicenter randomized, double-blind, placebo-controlled, parallel-group, fixed combination study (NAC-MD-01) in adult patients with uncomplicated essential hypertension. Supportive evidence for long term safety was provided in the form of an open label study NAC-MD-02.

2. Background

The prevention and management of hypertension are major public health challenges for the United States. Current control rates (SBP < 140 mm Hg and DBP < 90 mm Hg), though improved, are still far below the Healthy People goal of 50% [1]. Blood pressure (BP) elevation is usually multifactorial, making it very difficult, if not impossible, to normalize pressure by interfering with only a single pressor mechanism. This is one of the main reasons that 2/3rd of patients who achieve effective BP control require 2 or more antihypertensive drugs[2, 3].

Rational combination therapy should be based on deliberate co-administration of two or more carefully selected antihypertensive agents. This is achieved by combining agents that either interfere with distinctly different pressor mechanisms or effectively block counter-regulatory responses. From this perspective, combining a beta blocker with an angiotensin receptor blocker does not seem to be consistent with the goals of a rational combination therapy as they both primarily interfere with renin-angiotensin-aldosterone pathway. The Applicant however, suggests that nebivolol is different from other beta blockers and possess ancillary vasodilatory effects. For the combination of nebivolol and valsartan to be useful, the relative contribution of the proposed ancillary vasodilatory effect of nebivolol would be critical.

[1] Egan BM, Basile JN. Controlling blood pressure in 50% of all hypertensive patients: an achievable goal in the Healthy People 2010 Report? J Investig Med. 2003;51:373–385.
[2] Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, et al. Success and predictors of blood pressure control in diverse North American settings: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2002;4:393–404.
[3] Black HR, Elliott WJ, Neaton JD, Grandits G, Grambsch P, Grimm R, et al. Baseline characteristics and early blood pressure control in the CONVINCE trial. Hypertension. 2001;37:12–18.

During the IND stage, the Applicant had several meetings with the Agency to discuss the development of the proposed combination. The clinical review (Xiao) describes the regulatory history in detail and will not be discussed further in this review.

3. CMC

Based on the chemistry, manufacturing, and controls (CMC) and biopharmaceutics information provided in this submission, the CMC reviewer states that the information is adequate for the drug substance and drug product. The establishments for the commercial manufacturing, packaging and testing were inspected and were found to be acceptable. The Biopharmaceutics reviewer concludes that the dissolution method and acceptance criteria for batch release and stability testing (b) (4) (b) (4) are acceptable. The Applicant has satisfactorily addressed all the deficiencies that were communicated during the review and as such CMC recommends approval.

4. Nonclinical Pharmacology/Toxicology

There were no nonclinical studies submitted for this 505(b)(2) application. The Pharmacology/Toxicology reviewer concludes that the agents in this combination tablet (nebivolol/valsartan) have already undergone extensive nonclinical testing when they were reviewed previously with the original NDAs and recommends approval.

5. Clinical Pharmacology

The clinical pharmacology review states that the clinical pharmacology information submitted to the application is sufficient to characterize and bridge the exposure of nebivolol/valsartan free combination with the FDC drug product. The review concludes that there are no outstanding clinical pharmacology issues that preclude approval. No agreement has been reached with Applicant about final labeling.

The key findings are briefly described below:

1. The FDC and nebivolol/valsartan free combination were bioequivalent, with the 90% confidence intervals of the geometric mean ratios for C_{max} and $AUC_{0-\infty}$ within the 80 - 125% range for both nebivolol and valsartan.
2. There is no clinically relevant food effect on the pharmacokinetics of nebivolol or valsartan when administered as FDC.
3. Single- and multiple-dose drug interaction studies showed that the co-administration of nebivolol and valsartan resulted in lower maximum plasma drug concentration (C_{max}) for nebivolol (~ 45% decrease) but no significant changes to total systemic exposure (AUC) when compared to nebivolol administered alone.
4. Data from the ambulatory blood pressure monitoring (ABPM) sub-study in trial NAC-MD-01 showed that the relationship between change from baseline in heart rate and C_{max} is shallow for FDC 20/320 and nebivolol 40 mg indicating that the lower C_{max} for

nebivolol when administered as FDC is unlikely to result in improved bradycardia associated tolerability.

5. Both nebivolol and valsartan as monotherapies exhibit a shallow dose-response relationship for their antihypertensive effects. Maximum effects are approached with a dose of 10 mg for nebivolol and 80 mg for valsartan respectively. The results from various combinations of the FDC are in agreement with what was observed from the dose-response trends for the individual components.

6. Clinical Microbiology

There are no specific clinical microbiology issues in the current submission.

7. Clinical/Statistical Efficacy

A detailed description of the clinical studies and results are presented in the clinical (Xiao) and statistical reviews (Kordzakhia). I fully agree with interpretation and recommendations of the reviewers and as such only relevant aspects will be presented briefly in this review.

Pivotal Trial Design:

The phase III trial (Study NAC-MD-01) was a multicenter, double-blind, randomized, placebo-controlled, parallel group fixed-dose combination study of 8-week duration (double-blind phase).

The study consisted of 1 week for screening followed by a single-blind, placebo washout/run-in period of up to 6 weeks, an 8-week double-blind treatment period, and a 1-week down-titration period.

At the end of the single-blind placebo washout/run-in period, patients (N = 4159) who met the entry criteria for this study were randomized in a 2:2:2:2:2:2:2:1 ratio to 1 of 8 double-blind treatment groups: the starting double-blind doses were FDC 5/80 mg, FDC 5/160 mg, FDC 10/ 160 mg, Nebivolol 5 mg monotherapy, Nebivolol 20 mg monotherapy, Valsartan 80 mg monotherapy, Valsartan 160 mg monotherapy, or placebo. All doses were doubled after 4 weeks to the final assigned treatment groups of FDCs 10/160 mg, 10/320 mg, 20/320 mg respectively and monotherapies of Nebivolol 10 mg, Nebivolol 40 mg, Valsartan 160 mg, Valsartan 320 mg, or placebo. Approximately 90% of the patients completed the double-blind treatment period, with no specific imbalances in the dropout by treatment.

The following are the key findings:

- All the monotherapy and FDC treatment arms demonstrated significant reductions in diastolic blood pressure (DBP) and systolic blood pressure (SBP) compared to placebo after 8 weeks period.

- Based on the pre-specified primary statistical analysis, the FDC 20/320 mg was statistically superior to both monotherapies (Nebivolol 40 mg and Valsartan 320 mg) as measured by the mean reduction in the trough seated DBP. The observed treatment difference between the FDC 20/320 mg and Valsartan 320 mg is -4.4 mmHg (-5.4, -3.3), while the treatment difference compared to Nebivolol 40 mg is -1.2 mmHg (-2.3,

-0.1). The ABPM sub-study findings also report similar findings for 24 hour DBP [FDC 20/320 mg vs Nebivolol 40 mg: -1.6 mmHg (-3.7, 0.6)]. Essentially, the trial ensures at least 0.1 mmHg lowering with the FDC compared to Nebivolol 40 mg. Further, the clinical meaningfulness of the treatment effect achieved with the FDC 20/320 mg compared Nebivolol 40 mg becomes highly questionable in clinical practice, especially with a mean estimated within-subject variability of 5.6 mmHg. The impact of this small difference in treatment effect is also reflected in the lack of separation between the two treatment arms for the probability of achieving the DBP goals (<90 mmHg or <80 mmHg) as a function of baseline DBP.

- The mean reduction in SBP (secondary efficacy measure) with the FDC 20/320 mg was greater than the reductions observed with Nebivolol 40 mg and Valsartan 320 mg (treatment effect of ~3 mmHg for both comparisons). The mean estimated within-subject variability was 5.3 mmHg.

- Looking across some of the contemporary combination antihypertensive programs, the primary efficacy findings from the current application represent the smallest treatment effect (statistically significant) for the combination over the highest approved dose for one of the components (see Table 14 of the Clinical Review by Xiao). Further, NAC-MD-01 also happens to be the largest phase 3 trial conducted for a combination antihypertensive trial.

- Exploratory analyses did not identify any subgroups of interest (eg., diabetics, elderly or African Americans, etc) for which the FDC displayed a clinical significant greater reduction in blood pressure compared to the nebivolol 40 mg.

- A comparison of the cumulative distribution curves of the blood pressure effects for FDC 20/320 mg and Nebivolol 40 mg do not indicate a subgroup of hyper-responders to the FDC.

Reviewer's Comment:

The clinical relevance of the treatment effect with the FDC of nebivolol/valsartan compared to the highest approved dose of nebivolol (40 mg) is questionable. In general I agree with the assessment of both the clinical and statistical reviewers on this aspect. The following are my specific reasons:

- *The Division has consistently asserted that the comparison of the FDC to the highest approved dose of monotherapies is most relevant for regulatory action. This expectation, I believe, is aimed to deter development of combination products with similar mechanism of actions, which may satisfy the combination rule at the submaximal doses but may fail to demonstrate the same when compared to the maximal doses of one of the components. This avoids creation of an unnecessary step in a patient's care that simply delays the time to reach an adequate blood pressure goal. The primary efficacy results of NAC-MD-01 highlight this type of concern, as evident from the treatment effect of 1.2 mmHg with the FDC 20/320 mg compared to Nebivolol 40 mg. Hence, absent of other advantages, FDC of nebivolol/valsartan is*

not a meaningful alternative for treating hypertension in patients who are candidates for receiving nebivolol monotherapy.

- *The Applicant contends that we should consider the benefit of the FDC compared to valsartan monotherapy. While the data supports this inference, there is no regulatory precedence for the approval of the FDC combination based on the demonstration of clinically relevant treatment effect compared to only one of the components of the combination. Further, this would be contrary to the spirit of the combination rule that require demonstration of benefit with the FDC over both components as monotherapies. It is clearly evident from NAC-MD-01 that treatment with Nebivolol 40 mg results in relatively greater reduction in blood pressure compared to treatment with Valsartan 320 mg (ΔDBP: 7.5 mmHg versus 4.3 mmHg)[4]. In such a scenario, absent other advantages, switching to nebivolol monotherapy is likely to provide similar benefit to that expected with the FDC.*
- *In the current program, the highest dose of the FDC did not include the highest approved dose of nebivolol. The Applicant makes a case that their comparison of the highest dose of FDC (20/320 mg) to Nebivolol 40 mg is conservative. A post hoc estimate for comparison to nebivolol 20 mg (Week 4 assessment from the Nebivolol 40 mg treatment arm; not evaluated as a separate arm in Phase 3) shows a treatment effect of 2.2 mmHg (DBP). This incremental effect is small and does not alleviate the concerns about the clinical relevance and is consistent with the Applicant's prior expectation. In a written response to the Agency during the IND, the Applicant stated that an additional DBP reduction of 1 to 3 mmHg with Nebivolol 40 mg compared to Nebivolol 20 mg is expected and that this does not represent a significantly better BP response[5]*
- *There are no indications of subgroups that may preferentially benefit with the FDC.*
- *The dose-response relationship for the FDC is shallow (see table below) and is a reflection of the dose-response relationships for the monotherapies.*

Change from baseline in trough seated blood pressure for the FDC in NAC-MD-01

Treatment Group	***DBP, mmHg (95% CI)***	***SBP, mmHg (95% CI)***
FDC 5/80 vs Placebo*	*-7.2 (-8.4, -5.9)*	*-8.3 (-10.3, -6.3)*
FDC 20/320 vs Placebo	*-8.7 (-10.0, -7.3)*	*-9.9 (-12.1, -7.7)*
Nebivolol 40 mg vs Placebo	*-7.5 (-8.8. -6.1)*	*-7.0 (-9.2. -4.8)*

**Week 4 data only*

Treatment with FDC 5/80 mg for 4 weeks resulted in average blood pressure reduction of 7.2/8.3 mm Hg (DBP/SBP corrected for placebo), while treatment with FDC 20/320

[4] Source: Clinical Study Report Table 11.4.1.1-1. (pg. 124)
[5] Minutes of the Teleconference on Feb 15, 2011 for P-IND 109771 (Page 4 of 6): "The rationale for considering 20 mg as the highest dose of nebivolol in the study is that the dose response is shallow, with DBP reductions of 1 to 3 mm Hg with each dose increase above 20 mg and the 40mg dose does not provide a significantly better BP response."

mg by week 8 resulted in a treatment effect of 8.7 /9.9 mmHg (DBP/SBP corrected for placebo). A 4-fold increase in the dose of both the drugs resulted on average 1.5/1.6 mm Hg incremental benefit. As such the utility of FDC 20/320 mg over FDC 5/80 mg is questionable. This is likely due to the saturation of a common pathway. Addition of the two agents at low dose is providing a similar effect to that achieved with the highest dose of the more potent monotherapy.

6. Safety

The clinical review concludes that the safety profile of the FDC is acceptable for the proposed indication (for details see Clinical Review by Xiao). The following is a brief description of the tolerability profile specifically reflecting the nebivolol component:

- In general the incidence of bradycardia and fatigue were higher with nebivolol 40 mg compared to the FDC 20/320 mg. However, the incidence was generally low for nebivolol 40 mg (~5%).
- The incidence of premature discontinuation of the study drug associated with bradycardia in the double-blind phase with Nebivolol 40 mg was numerically greater compared to FDC 20/320 mg. It should be noted that the incidence of such discontinuations was in general very low (1.5% with Nebivolol 40 mg). Further, none of the 11 bradycardia events associated with premature discontinuation of Nebivolol 40 mg had clinical symptoms reported on the case report forms. These were driven by the protocol stipulated discontinuation for a sitting pulse of <50 bpm.

Reviewer's Comment:
There is no evidence of tolerability advantage with the FDC compared to either of the monotherapies.

7. Advisory Committee Meeting

The clinical relevance of a statistically significant but small treatment effect with the FDC over the highest marketed dose of one of its components was identified as a critical regulatory issue very early in the review cycle and was the primary reason for seeking the input of an Advisory Committee. On September 09, 2014, the Cardiovascular and Renal Drugs Advisory Committee met to discuss this application. The Addendum to Clinical Review by Xiao (12/05/2014) outlines the proceedings of the Advisory Committee and the follow-up with the Applicant thereafter. While the Committee was not unanimous in its decision whether to approve the FDC or not (Yes = 4 – No = 6), they generally agreed that absent other advantages, combination products must be required to provide a minimum systolic blood pressure effect. The committee did not think that FDC provided any advantage on tolerability. Further, if approved, the committee felt that the FDC would be best served as a replacement therapy for patients already on the two single agents. Following the Advisory Committee Meeting, the Division invited the Applicant to identify responder population that would benefit from the FDC. The information provided by the Applicant was not persuasive enough to justify the approval of the FDC for a subgroup of patients that would derive significantly greater benefit that could be achieved with either of the monotherapies.

8. Pediatrics

The sponsor did not conduct pediatric studies. Safety and efficacy have not been established in the pediatric population for either monotherapy. In order to meet the requirements of the Pediatric Research Equity Act (PREA), the Applicant is requesting a full waiver of pediatric studies in patients ages 0 to 17 years. The basis for requesting full waiver is: i) the prevalence of pediatric hypertension is low, and ii) FDC antihypertensive products are not currently recommended for routine use in pediatric patients. In general, the Division, by long-standing policy, does not require pediatric studies for combination antihypertensive products and as such the application should qualify for waiver.

9. Other Relevant Regulatory Issues

- **Financial disclosures:** There are no significant issues related to financial disclosure.
- **Clinical Inspection Summary:** Three domestic clinical investigator inspections (Sites 1011, 1154 and 1094) were conducted in support of NDA 206302. Sites 1011 and 1154 were chosen for inspection because of relatively high enrollment and high treatment effect size in the FDC treatment arm, while Site 1094 had high enrollment and a sponsor complaint issued in 2009 in which the site was terminated due to GCP noncompliance for a different application. No regulatory violations were found during the inspection of Site 1094, and the inspection was classified NAI. Although regulatory violations were noted at Site 1011 and Site 1154, they are unlikely to significantly impact the primary efficacy or safety analysis for this study. Therefore, the data from this study may be considered reliable.
- **505(b)(2) Requirements:** The Applicant owns the data for nebivolol, hence the application of 505(b)(2) in this application pertains to valsartan. The Applicant is relying on the Agency's previous findings of safety and effectiveness for the listed drug Diovan® based on NDA 20-665 for 80 and 160 mg oral capsules and NDA 21-283 for 80, 60 and 320 mg oral tablets, both submitted by Novartis Pharmaceutical Corporation. In particular, the Applicant is relying on the nonclinical portions of the application and section of the approved package insert. This is justified by the PK bridging between FDC 20/320 mg and Valsartan 320 mg.

10. Labeling

- **Proprietary Name:** The proposed proprietary name Byvalson® has been reviewed by the Division of Medication Error Prevention and Analysis and is found acceptable from both a promotional and safety perspective.

11. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action:**
  Based on the review of information submitted to the application and the input from the Cardiovascular and Renal Products Advisory Committee meeting, I do not believe that that there is a place for the FDC of nebivolol and valsartan either as an initial therapy or as an add-on therapy in patients whose blood pressure is not adequately controlled on monotherapy. The benefits proffered with the FDC can be achieved with nebivolol monotherapy. The FDC does not provide tolerability advantage over nebivolol monotherapy. Approval of the FDC as a replacement therapy will only serve to legitimize a combination with weak mechanistic basis and unnecessarily delay patients from receiving other antihypertensive treatments that have greater treatment effects. Moreover, the Applicant has not provided any information in support of the FDC for replacement therapy claim such as data demonstrating improved adherence. Hence, I recommend **Complete Response** as the appropriate regulatory action for this application.

- **Risk Benefit Assessment**
  The clinical program for the FDC of nebivolol and valsartan clearly demonstrated that numerically greater blood pressure reduction can be achieved with the FDC compared to that achieved with the highest dose of either monotherapies. Even though the clinical relevance of the small incremental treatment effect with the FDC is questionable, based on the understanding of the continuous relationship between blood pressure and cardiovascular disease outcomes from epidemiology, an incremental CV benefit can be envisioned. However, availability of such treatment options are more likely to result in delaying patients from receiving better treatments and getting to blood pressure goals in clinical practice. The risk of delay to achieve and maintain goal is of greater consequence. In addition, there is a potential for off-label use of the FDC in heart failure. Valsartan is approved for treatment of stable NYHA class II or III heart failure. Beta blockers such as metoprolol and carvedilol are one of the mainstays for the treatment of chronic heart failure. Nebivolol, a beta blocker, is not approved for the treatment of heart failure (NYHA Class II – III). At the Cardiovascular and Renal Products Advisory Committee Meeting on 01/11/2010, nebivolol received a unanimous negative vote for the treatment of chronic heart failure (Yes – 0; No – 8). Approval of the FDC may either promote the inappropriate use in the treatment of chronic heart failure or may lead to suboptimal dosing of either metoprolol or carvedilol in heart failure patients who may be receiving the FDC instead of valsartan monotherapy. If a decision is made by the signatory to provide the FDC of nebivolol/valsartan as an option for the treatment of hypertension as initial therapy, then based on the dose-response information, doses greater than FDC 5/80 mg do not warrant approval. In addition, strong labeling instruction should be included to encourage physicians to either switch to an alternate treatment or add another class of agent if the goal is not reached within a month of treatment.

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/s/

RAJANIKANTH MADABUSHI
12/17/2014
CDTL Memo

Addendum to Clinical Review of NDA 206302

Background: On February 24, 2014, Forest Laboratories, Inc. submitted NDA 206302 for nebivolol/valsartan fixed dose combination tablets (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg) for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy. In my original clinical review, dated August 8, 2104, I indicated that I had concerns with the product's efficacy, and specifically the finding that valsartan had little effect on diastolic blood pressure when added to the highest marketed dose of nebivolol (least square mean difference of 1.2 mmHg, 95% CI of 0.1 to 2.3 mmHg). Because of this finding, I stated in my review that I wanted to hear the Advisory Committee (AC) discussion before making a recommendation on approval. This addendum includes a summary of the AC meeting discussion. It also contains my review of analyses that were submitted by the applicant after the AC meeting. According to the applicant, these analyses provide evidence of a high-treatment-effect responder subgroup.

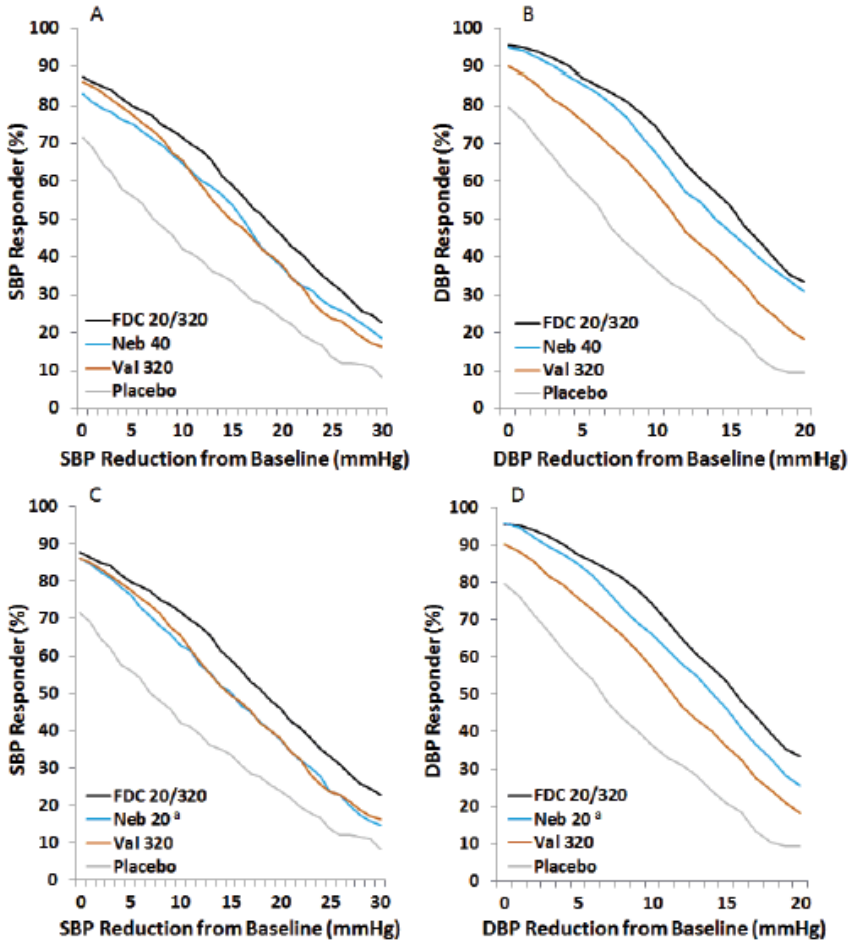
AC Meeting Discussion: On September 9, 2014, the Cardiovascular and Renal Drugs Advisory Committee met to discuss the application. As reported in the internal "Quick Minutes" for the meeting:

1) The AC generally agreed that absent other advantages, it was reasonable to require that an antihypertensive agent provide some minimum blood pressure effect and that the effect should be based more on systolic blood pressure than diastolic blood pressure.
2) The AC also agreed that the combination product was more effective in reducing blood pressure than its monocomponents; however, there was no consensus as to whether the observed treatment effect was clinically relevant.
3) Overall, the AC did not think that the development program demonstrated that the FDC was better tolerated than 40 mg or 20 mg of nebivolol.

When asked whether the FDC product should be approved for the treatment of hypertension, four members voted "yes" and six voted "no". Those who voted "yes" cited the drug's safety, a much better blood pressure response than suggested by the mean in some patients, and/or felt that the size of the treatment effect on systolic blood pressure seemed clinically relevant. Those who voted "no" cited, among other reasons, the small treatment effect, the availability of other agents with a larger effect size, and/or concern that approving a combination product with a very small effect would prevent patients from getting to goal efficiently or at all.

Applicant's submissions dated October 3rd and November 7th: At the September 9th AC meeting, the applicant presented an analysis showing that a greater percentage of subjects achieved a 20/10 mmHg reduction in blood pressure in the FDC arm than in the nebivolol or valsartan monotherapy arms. Following the AC meeting the Division invited the applicant to make the case that there were responders who experienced a reduction in blood pressure that was considerably greater than the mean difference between the combination and individual components. The Division noted that at the AC meeting, "Dr. White presented material on some arbitrary effect size, but we will be more interested in a treatment of this issue that is not focused on some arbitrary and post hoc selection. We believe that you briefly displayed cumulative distribution curves for effects of various treatments; we would be particularly interested in seeing those as well as how you interpret them as indicative of a responder group."

In response, the applicant submitted additional analyses on October 3, 2014. The figure below, taken from the applicant's submission, shows the cumulative distribution of the proportion of patients achieving discrete reductions in systolic or diastolic blood pressure. In these analyses, the FDC curve appears to be shifted to the right of the monotherapy curves but is otherwise parallel in nature; hence the analyses do not suggest a responder population.



Continuous responder analysis for the FDC 20/320 mg, nebivolol 40 mg , valsartan 320 mg and placebo. The upper left panel (A) shows the proportion achieving reductions from baseline in SBP. The upper right panel (B) shows the proportion achieving reductions from baseline in DBP. The lower left panel (C) and the lower right panel (D) show the same proportions, however include nebivolol 20 mg instead of nebivolol 40 mg. These curves directly represent actual data and are not modeled.

a. Data obtained after 4 weeks of treatment.

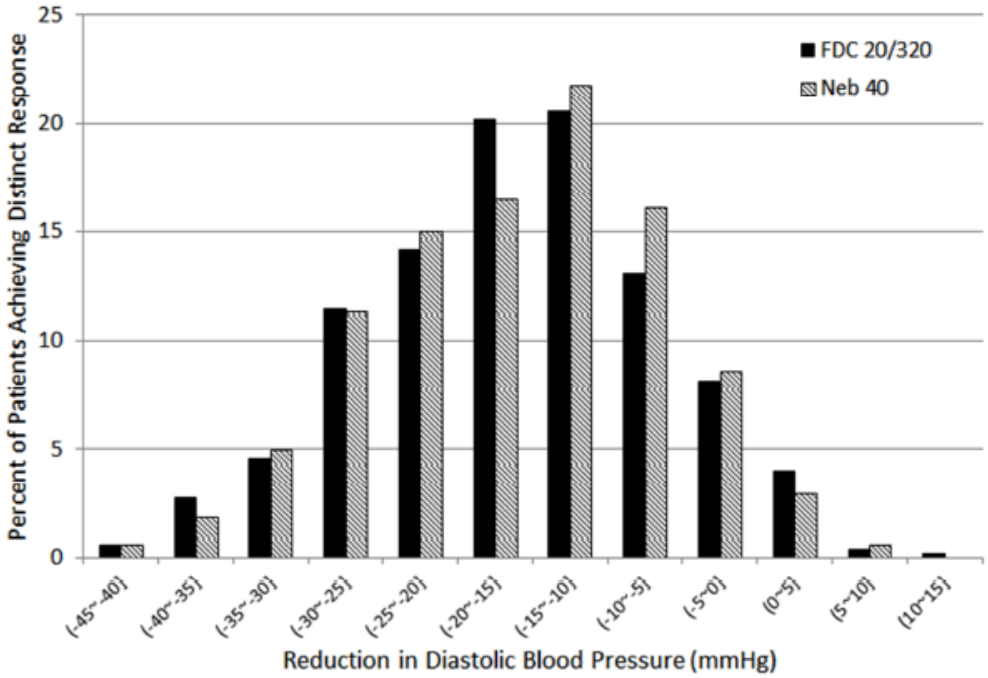
Figure 1. Cumulative Distribution of the Proportions of Patients Achieving Discrete Reductions in Blood Pressure

Source: Figure 3, Applicant's submission dated October 3, 2014

During a teleconference on October 15, 2014, the Division informed the applicant that the submitted analyses did not suggest the presence of a responder population. In response, the applicant submitted a new analysis, as well as an analysis that was previously submitted to the

Agency. The new analysis (Figure 2) shows the full distribution of DBP responders at 5 mmHg intervals after shifting nebivolol 40 mg by the mean treatment effect of 1.2 mmHg. The previously submitted analysis (Figure 3) shows the distribution of the proportion of patients with changes from baseline in DBP using 5 mmHg intervals between -9 mmHg and +14 mmHg, and bins subjects with changes of -10 mmHg or more on the left side of the histogram and those with changes greater than or equal to + 15 mmHg on the right.

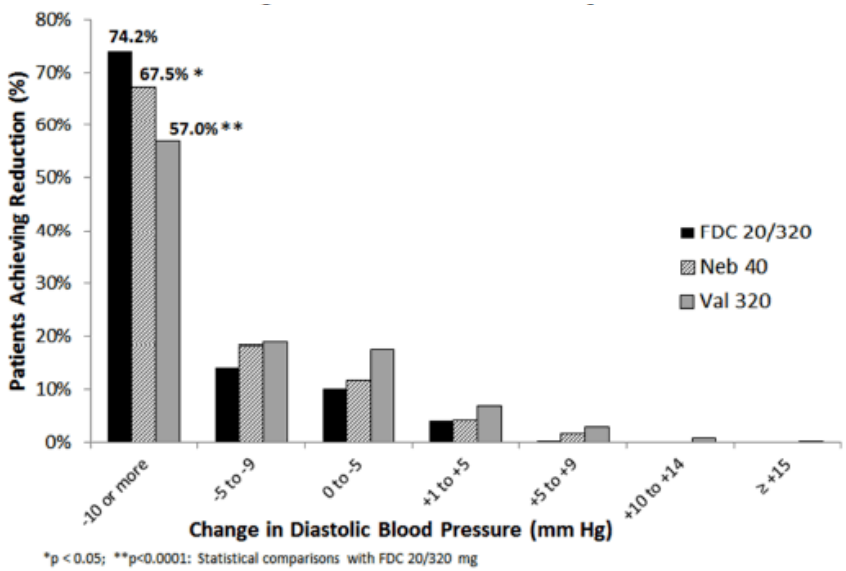
According to the applicant, the new analysis suggests that the responder data shown in the previously submitted analysis are not simply a product of the mean treatment effect and that high-treatment-effect responders have been identified. However, according to Dr. Kordzakhia, the assigned FDA statistician, this interpretation is not justified and other interpretations are possible. Dr. Kordzakhia notes that the histogram of the FDC 20/320 arm is symmetric with a mode at approximately -15 mmHg, while the histogram for the nebivolol 40 arm has noticeable negative skewness with a mode at approximately -10 mmHg. Although there is some difference between the two modes, the means of the distributions are approximately equal. Hence, the analyses do not clearly demonstrate a responder population.



In this figure, all patients on nebivolol 40 mg had their diastolic blood pressure shifted by the mean value (1.2 mmHg) from the primary endpoint of Study NAC-MD-01. This figure shows the percent of patients achieving discrete reductions in diastolic blood pressure at 5 mmHg intervals. Black bars represent FDC 20/320 mg responders and cross-hatched bars represent shifted nebivolol 40 mg responders.

Figure 2. Distribution of the Proportion of Patients with Changes from Baseline in Diastolic BP at 5 mmHg Intervals: FDC 20/320 mg vs Nebivolol 40 mg after Shifting Nebivolol Patients by 1.2 mmHg

Source: Figure 3, Applicant's submission dated November 7, 2014



Distribution of changes from baseline in DBP at 5 mmHg intervals, comparing the FDC 20/320 mg versus nebivolol 40 mg and valsartan 320 mg once-daily at Week 8. This figure was also shown in a previous response from the Sponsor.

Figure 3. Distribution of the Proportion of Patients with Changes from Baseline in Diastolic BP at 5 mmHg Intervals

Source: Figure 4, Applicant's submission dated November 7, 2014

Reviewer's Recommendation on Approval: Based on my original review of the application, the discussion at the AC meeting and the applicant's subsequent analyses which failed to demonstrate a responder population, I do not recommend approval of this product for the treatment of hypertension. I do not believe that the development program provides evidence of a clinically meaningful difference in efficacy between the FDC product and nebivolol monotherapy at the highest dose level. The treatment effect is small, both in absolute terms and relative to the effect achieved with other marketed products, and hence approval of this product may delay and/or prevent patients from getting to blood pressure goals.

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/s/

SHEN XIAO
12/05/2014

ALIZA M THOMPSON
12/05/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206-302
Priority or Standard	Standard
Submit Date(s)	February 24, 2014
Received Date(s)	February 26, 2014
PDUFA Goal Date	December 24, 2014
Division / Office	DCRP/ODEI/OND
Reviewer Name(s)	Shen Xiao M.D, Ph.D
Review Completion Date	August 6, 2014
Established Name	Nebivolol/Valsartan
(Proposed) Trade Name	To be determined
Therapeutic Class	Antihypertensive (beta (β)-1 adrenergic receptor blocker combined with angiotensin II type 1 receptor blocker)
Applicant	Forest Laboratories, Inc.
Formulation(s)	Oral tablet
Dosing Regimen	Nebivolol/Valsartan: 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg
Indication(s)	Treatment of hypertension
Intended Population(s)	Adult patients with hypertension

Template Version: March 6, 2009

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Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CK	creatine kinase
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRP	C-reactive protein
CVA	cerebrovascular accident
DBP	diastolic blood pressure
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
FDC	fixed dose combination
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HCTZ	hydrochlorothiazide
HF	heart failure
ICH	International Conference on Harmonization
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
LOCF	last observation carried forward
LSM	least squares mean
LVH	left ventricular hypertrophy
MI	myocardial infarction
MRI	magnetic resonance imaging
NDA	New Drug Application
NS	not significant
OSI	Office of Science Investigation

PD	pharmacodynamics
PEY	person-exposure-year
PK	pharmacokinetic
PRA	plasma renin activity
PRC	plasma renin concentration
PTCA	percutaneous coronary angioplasty
QD	once a day
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SPA	special protocol assessment
TEAEs	treatment emergent adverse events
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

As discussed below, I have concerns with the efficacy data, but would like to hear the advisory committee discussion before making a recommendation on approval.

1.2 Risk Benefit Assessment

On February 24, 2014, Forest Laboratories, Inc. submitted NDA 206302 for nebivolol/valsartan fixed dose combination tablets (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg and 20/320 mg) for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy. In support of the proposed indication, the applicant conducted a large (N=4161), factorial, placebo-controlled, 8-week trial in patients with stage 1 or 2 hypertension and a 52-week single-arm, open-label trial.

The applicant's factorial trial was successful in demonstrating statistically significant greater reductions in mean seated diastolic and systolic blood pressure with fixed-dose combination (FDC) treatment as compared to the corresponding monotherapy groups. Compared to the highest marketed dose of valsartan, the nebivolol-valsartan FDC reduced diastolic blood pressure by an additional ~3.6 mmHg (FDC 10/160 mg) to 4.4 mmHg (FDC 20/320 mg) and systolic blood pressure by an additional ~ 3 mmHg (FDC 10/160 mg, 10/320 mg, and 20/320 mg). However, valsartan had little effect on diastolic blood pressure when added to the highest marketed dose of nebivolol (40 mg). The point estimate of the least square mean difference in diastolic blood pressure between the highest dose the nebivolol/valsartan FDC (20/320 mg) and the highest dose of nebivolol was only 1.2 mmHg with a 95% CI that spanned from 0.1 to 2.3 mmHg.

Both in absolute terms, and in comparison to what is achieved with other approved fixed-dose combinations, the added effect on blood pressure seems small. Moreover, on 24-hour ambulatory blood pressure monitoring, which captures effects on blood pressure during waking and sleeping hours, there was no obvious difference in systolic and diastolic blood pressure between the highest dose of the FDC product (20/320 mg) and the highest marketed dose of nebivolol (40 mg). Other analyses also raise questions about the utility of the different FDC dose strengths. In the applicant's factorial trial, dose-response relationships for the approved doses of the monotherapies and the proposed doses of the FDC product were shallow. The proposed dosage strengths of the FDC were not clearly distinguishable from each other with regard to blood pressure lowering effects and hence do not appear to represent a reasonable dose titration strategy.

The applicant contends that the benefits of adding valsartan to a "full dose" of nebivolol is demonstrated by (1) statistically significant reductions in diastolic and systolic blood pressure; (2) clinically meaningful reductions in systolic blood pressure which the applicant argues is a more accurate predictor of CV outcomes than reductions in diastolic blood pressure; (3)

statistically significant and favorable findings for blood pressure control; and (4) improved tolerability and safety of the FDC.

There is overall agreement on the first issue (i.e., that the trial was successful from a statistical perspective). In terms of the benefit of reducing systolic blood pressure vs. diastolic blood pressure, the available data and practice guidelines indicate that it is critical to reduce elevated diastolic and systolic blood pressures. As relates to blood pressure control rates, the benefit of adding valsartan to the highest dose of nebivolol appears to be modest. In addition, analyses conducted by FDA's statistical reviewer addressing the probability of reaching diastolic blood pressure goals as a function of baseline blood pressure do not suggest a difference between the highest dose of the FDC and the highest dose of nebivolol. It should also be noted that blood pressure control rates may not be the optimal metric for evaluating the efficacy of antihypertensives. Clearly, it is important to understand whether patients are likely to achieve blood pressure goals with a particular therapy; however, there is nothing magical about current thresholds, or for that matter, consensus on what these thresholds should be. We lower blood pressure to reduce the risk of cardiovascular events and we think the reduction in risk tracks with the baseline risk and the magnitude of blood pressure reduction.

As noted by the applicant, some analyses suggest that the FDC may be better tolerated than the highest marketed dose of nebivolol, a dose that may not be widely used:

- In the factorial trial, discontinuations and adverse events leading to discontinuations were reported at a higher rate on nebivolol 40 mg than on the highest dose of the FDC (13.7% vs 8.7% and 4.0% vs 1.6%, respectively).
- A dose-related increase in bradycardia was observed with nebivolol monotherapy but not with the FDC product. The incidence of bradycardia adverse events was greater at the highest dose of nebivolol (6.3%) than on the highest dose of the FDC product (2.5%). If one focuses on those adverse events that are likely to be of greater significance (i.e., those that led to discontinuation of therapy), there was a small difference between treatment arms which favored the FDC group, as discussed above.

While not the focus of this review, the shallow-dose response relationship for nebivolol clearly raises questions about the utility of the 40 mg dose of nebivolol and, specifically, whether the dose is unreasonable given a possible increased risk of bradycardia and the small increment in blood pressure reduction relative to lower doses of nebivolol. As relates to this review, if one concludes that the 40 mg dose is unreasonable, then it is important to consider how the highest dose of the FDC might fare against nebivolol 20 mg. One might speculate that the 20/320 mg dose of the FDC would provide a greater reduction in blood pressure than would nebivolol 20 mg (though again, there is the effect size issue); however there is no compelling reason to believe that the highest dose of the FDC would be associated with improved tolerability or safety relative to the 20 mg dose of nebivolol.

In summary, the data indicate that compared to the highest marketed dose of valsartan, the nebivolol/valsartan FDC reduces diastolic blood pressure by an additional ~3.6 mmHg (FDC 10/160 mg) to 4.4 mmHg (FDC 20/320 mg) and systolic blood pressure by an additional ~ 3 mmHg (FDC 10/160 mg, 10/320 mg and 20/320 mg). In contrast, adding valsartan to nebivolol

may not provide significant benefit in lowering diastolic blood pressure and one might reasonably ask whether the observed effect on blood pressure is too small to be useful. Some findings suggest that the highest dose of the FDC may have a better tolerability profile than the highest marketed dose of nebivolol, a dose that may not be widely used. These findings were mainly due to the higher incidence rate of bradycardia caused by the highest dose of nebivolol. Given these findings as well as the shallow dose-response relationship for the FDC product, there has been internal discussion about the possibility of approving a single dose of the nebivolol/valsartan FDC for use as add on therapy in patients who are not controlled on valsartan. There is no precedent for such an approach and further discussion is needed. There are no safety findings that would preclude approval.

1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Nebivolol/valsartan is a fixed-dose combination (FDC) tablet for the treatment of hypertension. Nebivolol is a vasodilatory beta-adrenergic receptor blocking agent. It was approved for the treatment of hypertension in the United States in 2007 (NDA 21-742). The mechanism of action behind the antihypertensive response to nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate; (2) decreased myocardial contractility; (3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers; (4) suppression of renin activity; and (5) vasodilation and decreased peripheral vascular resistance. In extensive metabolizers (most of the population) and at doses less than or equal to 10 mg, nebivolol is preferentially beta-1 selective. In poor metabolizers and at higher doses, nebivolol inhibits both beta-1 and beta-2 adrenergic receptors.

Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. It was approved for the treatment of hypertension in the United States in 1996 (NDA 21-283).

Five fixed doses of nebivolol/valsaran are proposed: 5/80, 5/160, 10/160, 10/320 and 20/320 mg. The recommended starting dose is 5/80 mg, or 5/160 mg, taken orally once daily. The dosage may be increased after 2 to 4 weeks of therapy at each step, up to a maximum dose of 20/320 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

A number of drugs are approved for the treatment of hypertension. The following table provides a list of approved antihypertensive agents.

Table 1: Approved drugs for chronic treatment of hypertension

Pharmacologic Class	Approved Drugs
aldosterone antagonists	eplerenone, **spironolactone**
alpha adrenergic blockers	**doxazosin**, phenoxybenzamine, phentolamine, **prazosin**, terazosin
angiotensin converting enzyme inhibitors	benazepril, **captopril**, **enalapril**, fosinopril, **lisinopril**, moexipril, perindopril, quinapril, **ramipril**, trandolapril
angiotensin II receptor blockers	**candesartan**, eprosartan, **irbesartan**, **losartan**, olmesartan, telmisartan, valsartan
arteriolar vasodilators	**hydralazine, minoxidil**
autonomic ganglionic vasodilators	mecamylamine
beta adrenergic blockers	**acebutolol**, **atenolol**, betaxolol, bisoprolol, **carvedilol**, carteolol, esmolol, labetolol, **metoprolol**, nadolol, penbuterol, **pindolol**, **propranolol**, timolol
catecholamine-depleting sympatholytics	deserpidine, **reserpine**
central alpha-2 adrenergic agonists	**clonidine**, guanabenz, guanfacine, **methyldopa**
calcium channel blockers	**diltiazem**, **verapamil**
dihydropyridine calcium channel blockers	**amlodipine**, **felodipine**, **isradipine**, **nicardipine**, **nifedipine**, **nisoldipine**
loop diuretics	bumetanide, ethacrynic acid, **furosemide**, torsemide
potassium-sparing diuretics	**amiloride**, triamterene
renin inhibitors	aliskiren
thiazide diuretics	chlorothiazide, **hydrochlorothiazide**, hydroflumethiazide, methyclothiazide, polythiazide
thiazide-like diuretics	**chlorthalidone**, indapamide, metolazone

(Source: FDA guidance-Guidance for Industry Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims, March 2011) Drugs shown in bold type have specific outcome data in either placebo-controlled or active-controlled trials as either primary or secondary treatment.

A number of fixed-dose combination products have also been approved for the treatment of hypertension. These include fixed-dose combinations of ACEIs/CCBs, ARBs/CCBs, ACEIs/HCTZ, ARBs/HCTZ, CCBs/beta blockers, beta blockers/HCTZ, centrally acting drug/HCTZ, aliskiren/HCTZ, aliskiren/valsartan (subsequently withdrawn from the market), and triple combinations (e.g., amlodipine/valsartan/HCTZ and amlodipine/benazepril/HCTZ). To date, however, no fixed-dose combination of a beta-blocker/ARB has been approved in the US.

2.3 Availability of Proposed Active Ingredient in the United States

Nebivolol was approved for the treatment of hypertension in the United States in 2007 (NDA 21-742, Bystolic). It is currently marketed in the United States at daily doses of 2.5, 5, 10, 20 and 40 mg. Valsartan was approved for the treatment of hypertension in the United States in 1996 (NDA 21-283, Diovan). It is currently marketed in the United States at doses of 80, 160, and 320 mg.

2.4 Important Safety Issues with Consideration to Related Drugs

Nebivolol, like other beta-blockers, carries a warning in labeling indicating that therapy should not be abruptly discontinued in patients with coronary artery disease because severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in this population following abrupt cessation of beta-blockers. In addition, beta-blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective beta-blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels. Other safety issues which largely reflect the physiologic effects of beta-receptor blockade include bradycardia, aggravation of cardiac conduction abnormalities, and aggravation of bronchospastic airway disease.

Valsartan, like other RAAS inhibitors, can cause hyperkalemia and also changes in renal function, including acute renal failure. The valsartan label carries a boxed-warning for fetal toxicity since RAAS inhibitors can cause injury and death to the developing fetus. There have also been post-marketing reports of hypersensitivity reactions including angioedema and rhabdomyolysis in patients treated with ARBs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-IND meeting was held on February 15, 2011 to discuss a 505(b)(2) application. At that meeting, the following issues were discussed:

- Although the highest approved dose of nebivolol is 40 mg, the sponsor proposed to compare the FDC of nebivolol and valsartan with nebivolol 20 mg and valsartan 320 mg as the highest monotherapy components. The sponsor stated that the 20 mg dose is as effective as the 40 mg dose and that the dose response is shallow, with DBP reductions of 1 to 3 mm Hg with each dose increase above 20. The sponsor also indicated that the overall incidence of adverse reactions and beta-blocker-related side effects, showed a substantial increase with the 20 and 40 mg doses as compared to the 10 mg dose. There was a discussion of possibly using the 20 mg dose of nebivolol and ruling out an effect as small as the imputed effect of 40 mg. However, the study plan was not finalized. The sponsor later agreed to compare the nebivolol/valsartan FDC of 20/320 mg with nebivolol monotherapy at the highest dose of 40 mg.
- The Division agreed that the proposed safety database, containing long-term safety collected on the free-tablet combination as well as short-term safety with the to-be-marketed FDC, was adequate to support an NDA. The Division also agreed that a thorough QT study was not needed.
- The Division indicated that a single dose, 2-way crossover trial would be needed to determine the formulation-effect when nebivolol and valsartan are administered as a free combination against the fixed dose combination (FDC). The study should be done in a fasted state with the maximum dose of both the drugs that is proposed in the FDC. This study should be prospectively powered to establish bioequivalence. The FDC and the individual doses should show reasonable bridging of exposures and not necessarily demonstrate bioequivalence by the strict limits (80-125%).

  A pre-NDA meeting that was scheduled for September 13, 2013 was cancelled and the sponsor's questions were addressed via written responses only. In that correspondence, the Division indicated that the single positive efficacy study, NAC-MD-01, could support NDA

filing and potential approval of nebivolol/valsartan FDC for the treatment of hypertension as add-on therapy, replacement therapy, and initial therapy. The Division questioned the utility of all of the proposed dosing strengths, based on the data that was provided, noting that the approved dosage strengths should be distinguishable from each other with regard to blood pressure effects and hence represent a reasonable strategy for dose titration. However, the Division did not comment specifically on the treatment effect of the highest dose of the nebivolol/valsartan fixed-dose combination relative to the highest dose of nebivolol.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

I did not identify any problems or major discrepancies which might confound the efficacy and safety evaluation of this product. The submission quality and integrity are acceptable.

3.2 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in full compliance with Good Clinical Practice and in accordance with the ethical principles of the Declaration of Helsinki, informed patient consent and Institutional Review Board approval.

According to the statistical reviewer, Dr. George Kordzakhia, there were no significant differences among the sites for the primary efficacy endpoint (reduction of diastolic blood pressure between the combination theray and each monotherapy). Nonetheless, three clinical sites are being inspected based on high enrollment and high treatment effect size including sites 1011, 1094 and 1154. Based on the report from Sharon Gershon in OSI, the data from site 1154 are acceptable. Results of inspections at the other two sites are pending.

3.3 Financial Disclosures

Information on financial disclosures is summarized in the following table.

Table 2: Financial disclosures: Studies NAC-MD-01 and NAC-MD-02

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 401		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There are no investigors who are sponsor employees.

There were two investigators who had financial information to disclose. FDA Disclosure Forms 3455 were provided, together with the corresponding background information, for investigators who reported financial interests or arrangements that existed with the applicant/sponsor. According to the applicant, the following steps were taken to eliminate any possibity of the investigator bias influencing the study results:

- A sub-investigator or monitor will assist or conduct certain parts of the research such as the Informed Consent process.
- Much of the study data will be recorded by a designee without a conflict interest.
- The study is blinded, multi-center and PROBE in design.
- The site will provide a limited number of subjects.

Based on the above information and the fact that there were more than 400 study sites (with no single site driving the efficacy findings), I do not think that the submitted financial disclosure information raises concerns about the the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review is pending. No issues that might affect the safety or efficacy evaluation of this product have been identified.

4.2 Clinical Microbiology

Based on Dr. Erika Pfeiler's review, the microbial limits specification for Nebivolol and Valsartan is acceptable; the product is recommended for approval from a product quality microbiology perspective.

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology or toxicology studies were submitted to support this 505 b (2) application.

4.4 Clinical Pharmacology

According to the clinical pharmacology review, the submitted studies are sufficient to characterize and bridge the exposure of nebivolol/valsartan free combination with the FDC drug product. The Office of Clinical Pharmacology recommends approval from a clinical pharmacology perspective.

4.4.1 Mechanism of Action

No mechanistic studies were conducted with the combination of these two products.

4.4.2 Pharmacodynamics

In multiple-dose studies in healthy adults, 320 mg of valsartan increased PRA and angiotensin II, whereas the FDC 20/320 mg neutralized the valsartan-induced increase in PRA and angiotensin II for 24 hours. Minimal decreases in urinary aldosterone excretion were observed with the FDC 20/320 mg. Heart rate was not affected by the administration of 320 mg of valsartan alone but, as expected, decreased with the administration of 20 mg of nebivolol alone or with the co-administration of 20 mg of nebivolol and 320 mg of valsartan.

In a placebo-controlled study in hypertensive patients, valsartan was associated with an increase in PRA (60-73% increase) whereas nebivolol was associated with a 51-65% reduction in PRA. Nebivolol in combination with valsartan reduced PRA (3-39% reduction). Nebivolol, valsartan, and FDC decreased plasma aldosterone levels. Administration of FDC to patients with essential hypertension results in a significant reduction of sitting, and standing diastolic and systolic blood pressure. Decreases in pulse rate from baseline were also observed in the FDC and nebivolol treatment groups.

4.4.3 Pharmacokinetics

The FDC and nebivolol/valsartan free combination were bioequivalent, with the 90% CIs of the geometric LS mean ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ within the 80 - 125% range for both nebivolol and valsartan. There is no clinically relevant food effect on the FDC. The

pharmacokinetics of both nebivolol and valsartan were proportional over the FDC dose ranges of nebivolol/valsartan 5/80 mg to 20/320 mg.

Single dose- and multiple-dose drug interaction studies showed that the coadministration of nebivolol and valsartan resulted in lower maximum plasma drug concentration (Cmax) for nebivolol (~45% decrease) but no significant changes to total systemic exposure (AUC) when compared to nebivolol administered alone. According to the clinical pharmacology reviewer, Dr. Bilal AbuAsal, these changes in systemic exposure are not considered clinically meaningful.

Please see detailed information from clinical pharmacology review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The nebivolol/valsartan FDC clinical program consisted of six phase 1 studies in healthy subjects and two phase 3 studies in patients with stage 1 or 2 essential hypertension. The phase 1 studies, which included biopharmaceutical studies and human pharmacokinetic and pharmacodynamic studies, are discussed in Section 4.3.3 and in the clinical pharmacology review. The table below provides an overview of the two phase 3 trials.

Table 3: Overview of the phase 3 efficacy and safety studies

Study #	Primary Objective(s) of the Study	Study Design and Type of Control	Test Product(s) and Dosing Regimen	Number of Subjects
NAC-MD-01	Evaluate the efficacy and safety of an FDC of nebivolol and valsartan compared to the monotherapy components and placebo in patients with stage 1 or stage 2 essential hypertension	Phase 3, multicenter, randomized, placeb ocontrolled, parallel-group study with 1 week of screening followed by a 6-week washout, single-blind placebo run-in phase followed by an 8-week double-blind treatment period, including 1 forced up-titration at Week 4, and a 1-week down-titration phase	*Test product*: FDC 5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, 20/320 mg *Reference therapy*: Nebivolol 5 mg, 10 mg, 20 mg, 40 mg; Valsartan 80 mg, 160 mg, 320 mg; placebo Patients were randomized in a 2:2:2:2:2:2:2:1 ratio to FDC, nebivolol monotherapy,valsartan monotherapy, or placebo. The dose was doubled after 4 weeks. At the end of 8 weeks of double-blind treatment, a 1-week double-blind down-titration period followed.	4161

NAC-MD-02	Evaluate the long-term safety of nebivolol and valsartan given as a free tablet combination in patients 18 years and older with stage 1 or 2 essential hypertension	Phase 3, multicenter, open-label, single-arm study with 1 week of screening followed by a 4-week washout, single-blind placebo run-in phase followed by a 52-week open-label treatment phase, and a 1-week down-titration phase	Treatment started with 5 mg nebivolol/160 mg valsartan combination; after 2 weeks, dose doubled (10/320 mg) for ≥ 4 weeks. If BP not met after ≥ 4 weeks, dose increased to 20/320 mg. For patients still not at goal after 10 weeks, HCTZ 12.5 mg/d added. If not at BP goal after additional 4 weeks with HCTZ, HCTZ dose doubled (25 mg/d). If not at BP goal after 14 weeks of HCTZ, patient was discontinued. After 52 weeks, there was a 1-week down titration.	810

(Reviewer table)

5.2 Review Strategy

For the efficacy and safety evaluation, I focused on the pivotal trial, Study NAC-MD-01, and the long-term study, Study-MD-02, as well as the approved labeling for the monothrapies. I also reviewed the published literature.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical program for the nebivolol/valsartan FDC was conducted in the United States. The design of the two Phase 3 trials is discussed in the following section.

5.3.1 Study NAC-MD-01

Study NAC-MD-01 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-arm, multiple-dose study of nebivolol and valsartan given as either FDC or separately as monotherapy in hypertensive patients who had a diagnosis of stage 1 or 2 essential hypertension. The study was conducted in 401 centers in the United States.

Important trial dates: The first patient was enrolled on January 6, 2012 and the last patient completed the study on March 15, 2013. The database lock date was June 7, 2013.

Efficacy endpoints: The primary efficacy endpoint was the change from baseline in seated trough DBP at Week 8 (FDCs 10/160, 10/320, and 20/320 mg compared with respective monotherapies).

The key secondary efficacy endpoint was the change from baseline in seated trough SBP at Week 8 (FDCs 10/160, 10/320, and 20/320 mg compared with respective monotherapies). The trial included numerous other secondary endpoints which also assessed effects on BP:

- Change in seated trough DBP from baseline to Week 4 (FDCs 5/80 and 5/160 mg compared with respective monotherapies)
- Change in seated trough SBP from baseline to Week 4 (FDCs 5/80 and 5/160 mg compared with respective monotherapies)
- Change in mean 24-hour ambulatory DBP from baseline to Week 8 (FDCs 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)

- Change in mean 24-hour ambulatory SBP from baseline to Week 8 (FDCs 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)
- Proportion of DBP responders, defined as seated trough DBP < 90 mm Hg at Week 8 (FDC 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)
- Proportion of DBP responders, defined as seated trough DBP < 80 mm Hg at Week 8 (FDC 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)
- Proportion of SBP responders, defined as seated trough SBP < 140 mm Hg at Week 8 (FDC 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)
- Proportion of SBP responders, defined as seated trough SBP < 130 mm Hg at Week 8 (FDC 20/320 mg compared with 40 mg nebivolol and 320 mg valsartan monotherapies)

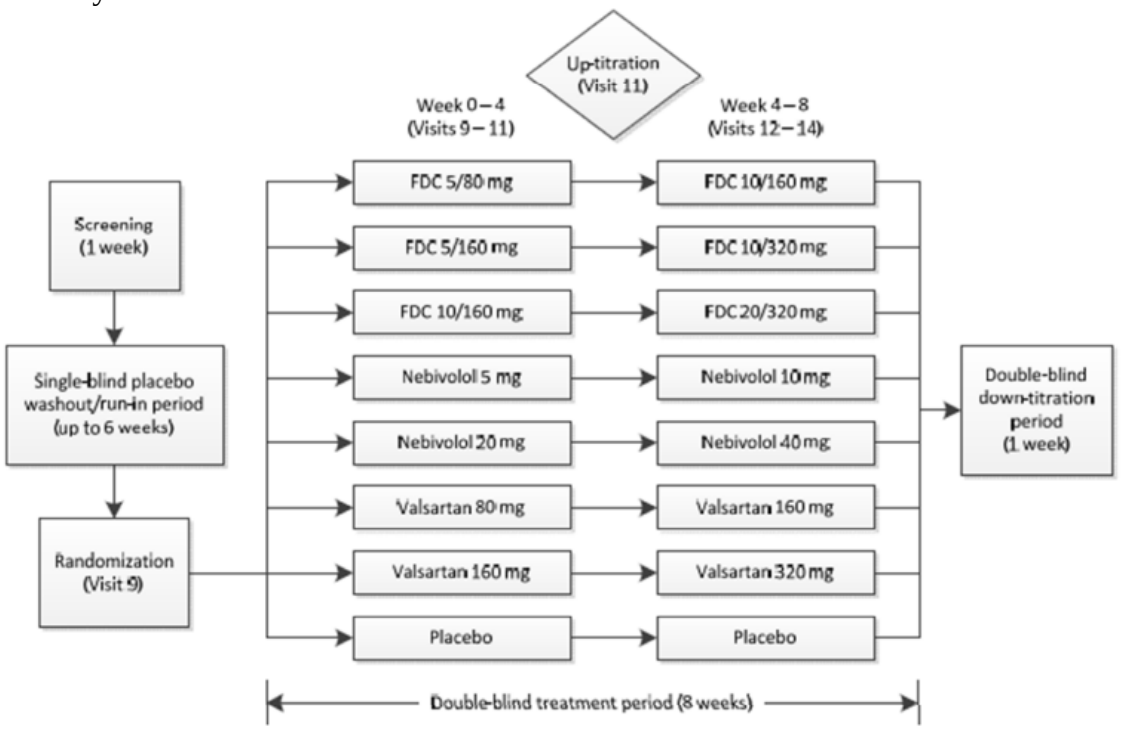
Entry Criteria: Key inclusion and exclusion criteria were as follows:

- Male or female outpatients, age 18 years and older
- At Screening, patients had to meet one of the following three criteria: 1) currently being treated for essential hypertension and at least 1 documented DBP value ≥ 90 mm Hg and < 110 mm Hg in their medical history; 2) newly diagnosed with essential hypertension and had never received treatment and had a mean seated DBP ≥ 95 mm Hg and < 110 mm Hg; 3) or previously diagnosed with essential hypertension and had not received antihypertensive medications for at least 4 weeks before Screening and had a mean seated DBP ≥ 95 mm Hg and < 110 mm Hg
- Seated pulse rate of at least 55 bpm at Screening, except for patients on beta-blockers
- Normal physical examination findings and electrocardiogram results or abnormal findings judged by the Investigator to be not clinically significant. Patients with QTcF ≥ 430 msec for male patients or ≥ 450 msec for female patients were excluded
- Patients with secondary hypertension (eg, renal artery stenosis, chronic renal disease, pheochromocytoma, primary hyperaldosteronism) or severe hypertension (mean seated SBP ≥ 180 mm Hg or mean seated DBP ≥ 110 mm Hg) were excluded

Study design: The study consisted of 1 week for screening followed by a single-blind, placebo washout/run-in period of up to 6 weeks, an 8-week double-blind treatment period with forced titration at 4 weeks, and a 1-week down-titration period.

At the end of the single-blind placebo washout/run-in period, patients who met the entry criteria were randomized in a 2:2:2:2:2:2:2:1 ratio to 1 of 8 double-blind treatment groups: the starting double-blind doses were FDC of nebivolol 5 mg and valsartan 80 mg (FDC 5/80 mg), FDC of nebivolol 5 mg and valsartan 160 mg (FDC 5/160 mg), FDC of nebivolol 10 mg and valsartan 160 mg (FDC 10/160 mg), nebivolol 5 mg monotherapy, nebivolol 20 mg monotherapy, valsartan 80 mg monotherapy, valsartan 160 mg monotherapy, or placebo. All doses were doubled after 4 weeks to the final assigned treatment groups as shown in the figure below.

Figure 1: Study NAC-MD-01 flow chart



(Applicant figure: CSR figure 9.1-1, page 39)

At the end of Week 8 or at early termination, subjects entered a 1-week, double-blind, down-titration period as described below:

- Patients who received nebivolol 40 mg had their nebivolol dosage reduced to 20 mg for 3 days, 10 mg for 3 days, and then placebo before discontinuing investigational product at Week 9.
- Patients who received nebivolol 20 mg, alone or in combination, had their nebivolol dosage reduced to 10 mg for 3 days and then placebo before discontinuing investigational product.
- Patients who received nebivolol 10 mg, alone or in combination, nebivolol was replaced by placebo before discontinuing investigational product.
- Patients who received nebivolol 5 mg, alone or in combination, nebivolol was replaced by placebo before discontinuing investigational product.

During down-titration, the dose of valsartan remained constant.

ABPM substudy: A substudy was conducted to assess 24-hour ABPM, sparse PK measurements, and biomarkers. According to the protocol, the substudy was to be conducted in 750 patients. ABPM assessments were to be performed prior to randomization and at week 8 of the double-blind treatment period.

Data analysis plan: The primary efficacy parameter was the change from baseline in mean seated trough DBP at Week 8 as measured by an Omron blood pressure monitoring device. An analysis-of-covariance model, with treatment group and diabetes status as factors and baseline value as a covariate, was used for treatment comparisons. The last observation carried forward

(LOCF) approach was used in the primary efficacy analysis. The primary efficacy analysis was based on the ITT Population. For each efficacy endpoint in each visit, BP was measured 4 times separated by a 2- or 5-minute interval in the morning between 8 and 10 am regardless of food; the mean value of the last 3 measurements constituted the value for that visit.

Safety analyses were based on the Safety Population.

Sample size calculation: A sample size of 500 patients per active arm would provide 95% power to detect a difference of 2 mmHg in seated DBP between the FDC of 20/320 mg and 40 mg nebivolol and between the FDC of 20/320 mg and 320 mg valsartan groups at a two-sided significance level of 0.05, assuming a standard deviation of 8 mmHg. Once the study was claimed positive, it would further provide 90% power—for 2 FDC doses of 10/160 and 10/320 mg with multiplicity adjustment by Hochberg procedure—to detect a difference of 2 mmHg in seated DBP between each FDC group and corresponding monotherapy groups at an overall significance level of 0.05 2-sided, assuming a standard deviation of 8 mmHg.

Statistical analysis plan dates and amendments: The statistical analysis plan was finalized and submitted to the Agency on February 8, 2012. The last patient completed the study on March 15, 2013. There were two SAP amendments:

Amendment #1 was made on December 10, 2012 and included the following changes:

- Added other secondary efficacy parameters, updated statistical analysis methods for these secondary efficacy parameters
- Added additional efficacy parameters and updated analysis methods for these efficacy parameters
- Added summaries for laboratory parameters BUN, creatinine and potassium by specific criteria and updated the criteria for potentially clinical significant laboratory tests.

Amendment #2 was made on April 8, 2013 after the last patient had completed the study. The only change made by this amendment was to add the change from baseline in seated trough pulse rate by visit up to Week 8 as an additional efficacy parameter.

Reviewer's comment: No changes were made to primary or key secondary endpoint analyses; these changes do not affect the interpretability of the efficacy data.

5.3.2 Study NAC-MD-02

NAC-MD-02 was an open-label, single-arm, multicenter study that assessed the long-term (52-week) safety of nebivolol/valsartan 5/160, 10/320, and 20/320 mg, given as free-tablet combinations, in patients with essential hypertension. The study was conducted in 133 centers in the United States.

Important trial dates: The first patient was enrolled on August 11, 2011 and the last patient completed the study on January 28, 2013. The database lock date was April 3, 2013.

Endpoints: The objective of this study was to evaluate the long-term safety of nebivolol and valsartan given as a free-tablet combination in patients 18 years and older with stage 1 or 2 essential hypertension. In addition, the study was designed to provide supportive information on the long-term maintenance of BP control. Efficacy assessments were performed, but the trial did not have a prespecified efficacy endpoint.

Safety assessments included AE recordings, clinical laboratory measures, vital sign parameters, ECGs, and physical examinations. For each safety parameter, the last assessment made before the first dose of open-label investigational product was used as the baseline for all analyses of that safety parameter. Each safety analysis for the open-label treatment phase was performed based on two sets of data: 1) all safety measurements, and 2) safety measurements before the initiation of rescue medication (HCTZ).

Efficacy assessments included:
- Change from baseline in trough seated DBP and SBP at each post-baseline visit up to Week 52
- Proportion of patients achieving a target BP goal (ie, < 140/90 mmHg or < 130/80 mmHg for type 2 diabetes patients)
- Proportion of DBP responders (ie, DBP < 90 mmHg or DBP < 80 mmHg for type 2 diabetes patients and/or ≥ 10 mmHg reduction from baseline in DBP)
- Proportion of SBP responders (ie, SBP < 140 mmHg or < 130 mmHg for type 2 diabetes patients and/or ≥ 10 mmHg reduction from baseline in SBP)
- Proportion of SBP responders meeting an SBP goal distinct from the goal described above (ie, SBP < 140 mmHg or < 130 mmHg for type 2 diabetes patients and/or ≥ 14 mmHg reduction from baseline in SBP)
- Change from baseline in standing DBP and SBP at Weeks 28 and 52
- Proportion of patients who were rescued (ie, the number of patients who were rescued divided by the number of patients in the ITT Population)

Entry Criteria: The key inclusion and exclusion criteria were similar Study NAC-MD-01.

Study design: The study consisted of 1 week of screening followed by a 4-week washout, single-blind placebo, run-in phase followed by a 52-week open-label treatment phase and a 1-week down-titration phase.

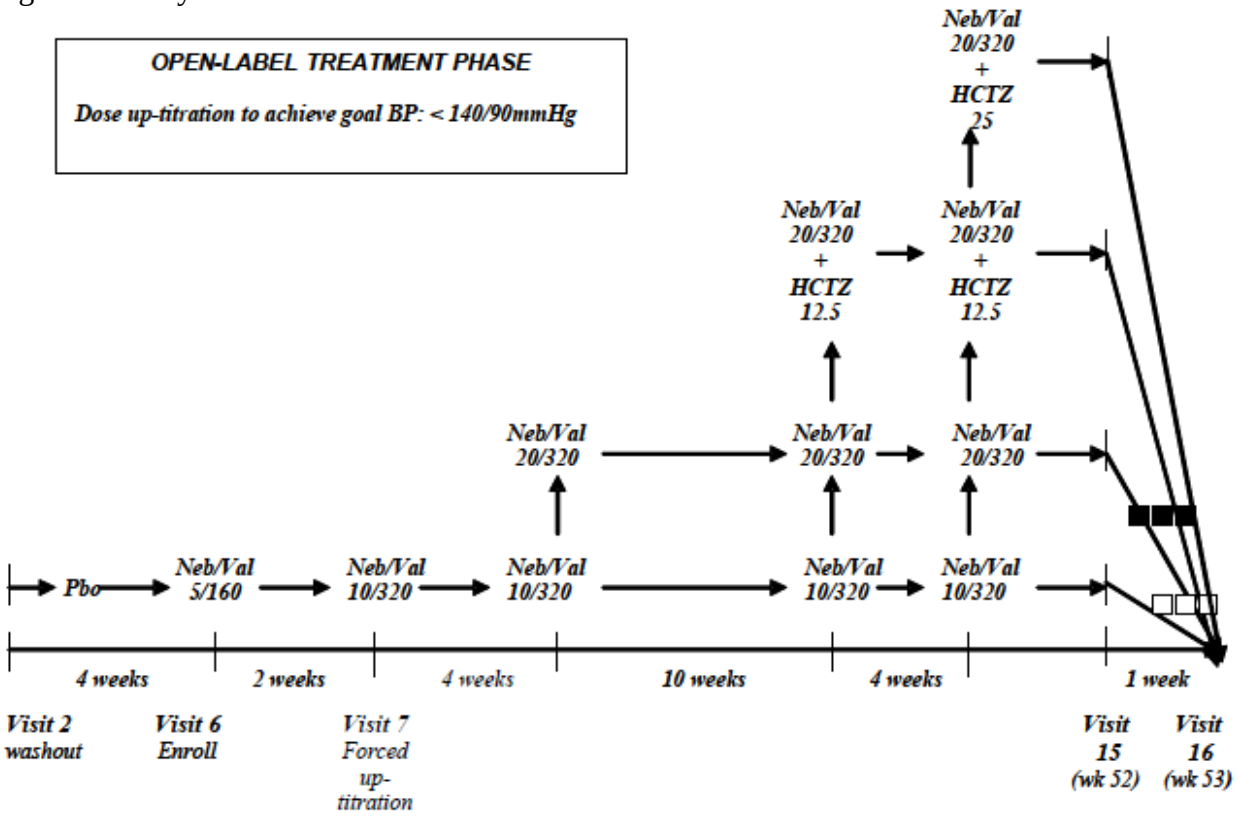
The 4-week washout, single-blind placebo run-in phase served as a washout phase for patients who were being treated and as an adjustment phase for patients to become familiar with the study medication (to increase compliance during the treatment phase). At the end of the single-blind placebo washout phase, patients still meeting the entry criteria were enrolled in the study and assigned to treatment using free tablets at a low-dose combination of 5/160 mg (5 mg of nebivolol and 160 mg valsartan).

After two weeks of treatment with the low-dose combination, the dose for all patients was doubled to 10/320 mg and continued for a minimum of 4 weeks. If the goal BP of < 140/90 mm Hg (< 130/80 mm Hg for type 2 diabetes patients) was not met after a minimum of 4 weeks of

treatment on the 10/320 mg dose, the dose was increased to 20/320 mg. For patients not at goal BP after being on the high-dose combination (20/320 mg) for a minimum of 10 weeks, HCTZ at a dose of 12.5 mg/day was added. If goal BP was still not achieved after an additional 4 weeks of treatment on this regimen, the dose of HCTZ was doubled to 25 mg/day. If goal BP was not achieved after a total of 14 weeks of treatment with HCTZ starting with the 12.5 mg/day dose, the patient was discontinued from the study. If a patient experienced symptoms of hypotension or displayed intolerance to study medication at any time during the treatment phase, the dose was reduced to the previous lower dose at the Investigator's discretion.

After 52 weeks of treatment, there was a 1-week down titration of nebivolol from 20 mg to 10 mg for 3 days followed by 5 mg for 3 days and then placebo, or from 10 mg to 5 mg for 3 days and then placebo, or from 5 mg decreased to placebo for 1 week (–1/+3 days) before discontinuing study medication. During down titration, the dose of valsartan and HCTZ (if added) remained the same. Upon early termination or completion of the study, the Investigator recommended a treatment to the patient or referred the patient to his or her primary care physician for customary standard care. An overview of the study design is summarized in the following figure.

Figure 2*:* Study NAC-MD-02 flow chart



Note: Goal BP was < 130/80 for patients with type 2 diabetes mellitus.
(Applicant figure: long term safety csr, figure 9.1-1, page 34)

6 Review of Efficacy

Efficacy Summary*:* The clinical development program for the fixed dose combination of nebivolol and valsartan included two phase 3 studies. Principle support for efficacy is provided by Study NAC-MD-01, an 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study that evaluated the efficacy of the combination of nebivolol and valsartan in comparison with each monotherapy and placebo in 4971 patients with essential hypertension. Data on the persistence of efficacy (long-term effects on BP) is provided by Study NAC-MD-02, an open-label, single-arm, 52-week safety and tolerability study in 810 hypertensive patients.

In Study NAC-MD-01, the highest-dose of the FDC (20/320 mg) led to statistically greater mean reductions in DBP and SBP as compared with the highest approved dose of nebivolol (40 mg) and valsartan (320 mg), thus meeting the trial's primary and key secondary endpoint. The other doses of the nebivolol/valsartan FDC (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg) also demonstrated statistically greater DBP reductions than their corresponding monotherapies; SBP reductions were also statistically greater in comparisons with corresponding monotherapies with one exception- the comparison of FDC 5/160 mg vs. valsartan 160 mg at the end of week 4. The percentage of patients achieving BP control (SBP < 140 mm Hg *and* DBP < 90 mm Hg for patients without type 2 diabetes, or SBP < 130 mm Hg *and* DBP < 80 mm Hg for patients with type 2 diabetes) was statistically significantly greater for all FDC doses at Week 4 and at Week 8 than the corresponding monotherapies.

There are several issues, however, that affect interpretation of these efficacy findings:

- **The size of the treatment effect on DBP**: Valsartan had little effect on diastolic blood pressure when added to the highest marketed dose of nebivolol (40 mg). The least squares mean difference in diastolic blood pressure between the highest dose the nebivolol/valsartan FDC (20/320 mg) and the highest dose of nebivolol was only 1.2 mmHg with a 95% CI of 0.1 to 2.3 mmHg. The fact that this finding was statistically significant (p =0.03) is likely a reflection of the trial's large sample size. While sample sizes of ~200 subjects per treatment arm are not uncommon in FDC antihypertensive trials (see Table 14), the applicant's trial included ~4000 subjects overall with approximately 500 subjects per treatment arm. While the applicant has satisfied the combination rule, it is important to ask whether some increment in blood pressure reduction is too small to be considered clinically meaningful. The availability of other FDC antihypertensives that appear to provide greater blood pressure effects over their constituent monotherapies, and the potential delay in the use of these agents also needs to be considered.
- **No apparent difference on 24-hour ABPM**: 24-hour ABPM is considered an important indicator of blood pressure control. In this study, however, there was no statistically significant difference in systolic or diastolic blood pressure between the highest dose of the FDC product (20/320 mg) and the highest marketed dose of nebivolol (40 mg) even though the sample size (more than 100 patients per treatment arm) does not appear to be samller than the sample size for ABPM studies in other combination programs.

- **Uncertain results in some subgroups:** Subgroup analyses can be difficult to interpret; however, subgroup analyses raise questions about efficacy in key patient populations**.** Relative to the pairwise comparisons in subjects without diabetes, the reductions in blood pressure appeared to be smaller in the pairwise comparisons in subjects with diabetes and the point estimate for the reduction in blood pressure in the pairwise comparison for FDC 20/320 mg vs. nebivolol 40 mg favored nebivolol in diabetics. There was no difference in blood pressure reduction between FDC 20/320 mg and nebivolol 40 mg in Blacks. Finally, FDC 20/320 mg did not produce a greater reduction in SBP in patients ≥ 65 years old than its corresponding monotherapies.
- **Likelihood of achieving DBP goals by baseline blood pressure**: The percentage of subjects achieving DBP goals (< 90 mmHg or <80 mmHg) by baseline DBP was similar in the FDC 20/320 mg and Nebivolol 40 mg monotherapy groups. Though the applicant has requested a claim for use as intial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals, these findings do not appear to support such a claim.
- **Shallow dose-response relationship across the proposed dose strengths**: In the applicant's factorial trial, dose-response relationships for the approved doses of the monotherapies and the proposed doses of the FDC product were shallow. The proposed dosage strengths of the FDC were not clearly distinguishable from each other with regard to blood pressure lowering effects and hence do not appear to represent a reasonable dose titration strategy.

With regard to long-term effects on blood pressure control, significant reductions in blood pressure were observed during the 52-week study, Study NAC-MD-02, and these changes were similar in magnitude to the blood pressure reductions demonstrated in the 8-week pivotal trial. However, by week 52, 59.0% (296 of 502 patients) required the addition of HCTZ as a rescue medication for blood pressure control.

ln summary, the applicant's pivotal trial was successful from a statistical perspective; however the clinical significance of the efficacy findings remains unclear

6.1 Indication

The proposed indication is for the treatment of hypertension, alone or with other antihypertensive agents, to lower the blood pressure. The proposed uses include:

- Add-on therapy in patients whose blood pressure is not adequately controlled on monotherapy
- Replacement therapy (substitution for the titrated components)
- Initial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals

6.1.1 Methods

The two phase 3 trials were examined separately. Efficacy analyses focused on Study NAC-MD-01, an 8-week, multiple-dose, factorial study. Study NAC-MD-02, a 52-week, long-term, open label, safety study, provided supportive data on long-term maintenance of BP control.

6.1.2 Demographics

Demographic information for the pivotal trial, Study NAC-MD-01, is provided in this section; demographic data for Study NAC-MD-02 is provided in Section 7. As show in the table below, the average age was 51.3 years, 84.7% of subjects were white, and 55.5% were male. Approximately 15% of patients were diabetic, 10% Black or African American, and about 9% were 65 years of age or older. Baseline characteristics including age, sex, diabetes status, race, ethnicity, weight, height, and BMI were well balanced among the treatment groups in the overall study and in the ABPM sub-study.

Table 4: Study NAC-MD-01: Demographic and physical characteristics

Parameter	*Placebo (N = 277)*	*FDC 10/160 (N = 555)*	*FDC 10/320 (N = 555)*	*FDC 20/320 (N = 554)*	*NEB 10 (N = 555)*	*NEB 40 (N = 554)*	*VAL 160 (N = 555)*	*VAL 320 (N = 554)*	*Total (N = 4159)*
Age, years									
Mean ± SD	51.1 ± 10.4	50.9 ± 10.1	51.6 ± 9.8	50.8 ± 9.7	51.7 ± 10.2	51.5 ± 10.8	51.7 ± 9.9	52.1 ± 10.7	51.3 ± 10.2
n	277	555	555	554	555	554	555	554	4159
Age group, years, n (%)									
< 65	250 (90.3)	511 (92.1)	510 (91.9)	513 (92.6)	500 (90.1)	500 (90.3)	505 (91.0)	500 (90.3)	3789 (91.1)
≥ 65	27 (9.7)	44 (7.9)	45 (8.1)	41 (7.4)	55 (9.9)	54 (9.7)	50 (9.0)	54 (9.7)	370 (8.9)
Sex, n (%)									
Male	148 (53.4)	300 (54.1)	315 (56.8)	313 (56.5)	307 (55.3)	297 (53.6)	333 (60.0)	295 (53.2)	2308 (55.5)
Female	129 (46.6)	255 (45.9)	240 (43.2)	241 (43.5)	248 (44.7)	257 (46.4)	222 (40.0)	259 (46.8)	1851 (44.5)
Diabetic, n (%)									
Yes	40 (14.4)	81 (14.6)	88 (15.9)	89 (16.1)	82 (14.8)	86 (15.5)	84 (15.1)	88 (15.9)	638 (15.3)
No	237 (85.6)	474 (85.4)	467 (84.1)	465 (83.9)	473 (85.2)	468 (84.5)	471 (84.9)	466 (84.1)	3521 (84.7)
Race, n (%)									
White	231 (83.4)	464 (83.6)	475 (85.6)	474 (85.6)	452 (81.4)	471 (85.0)	481 (86.7)	475 (85.7)	3523 (84.7)
All other races	46 (16.6)	91 (16.4)	80 (14.4)	80 (14.4)	103 (18.6)	83 (15.0)	74 (13.3)	79 (14.3)	636 (15.3)
Black or African American	30 (10.8)	56 (10.1)	56 (10.1)	52 (9.4)	69 (12.4)	54 (9.7)	43 (7.7)	51 (9.2)	411 (9.9)
Asian	12 (4.3)	25 (4.5)	11 (2.0)	18 (3.2)	22 (4.0)	19 (3.4)	24 (4.3)	18 (3.2)	149 (3.6)
American Indian or Alaska native	2 (0.7)	7 (1.3)	6 (1.1)	2 (0.4)	4 (0.7)	3 (0.5)	3 (0.5)	3 (0.5)	30 (0.7)
Native Hawaiian or other Pacific Islander	0	0	3 (0.5)	3 (0.5)	1 (0.2)	3 (0.5)	1 (0.2)	2 (0.4)	13 (0.3)
Other	2 (0.7)	3 (0.5)	4 (0.7)	5 (0.9)	7 (1.3)	4 (0.7)	3 (0.5)	5 (0.9)	33 (0.8)
Ethnicity, n (%)									
Hispanic or Latino	113 (40.8)	252 (45.4)	239 (43.1)	231 (41.7)	206 (37.1)	220 (39.7)	207 (37.3)	216 (39.0)	1684 (40.5)
Non-Hispanic or Latino	164 (59.2)	303 (54.6)	316 (56.9)	323 (58.3)	349 (62.9)	334 (60.3)	348 (62.7)	338 (61.0)	2475 (59.5)
Weight, kg									
Mean ± SD	93.55 ± 20.65	91.06 ± 20.43	92.20 ± 20.03	92.17 ± 20.82	92.42 ± 21.18	91.33 ± 21.25	92.32 ± 20.85	92.11 ± 20.79	92.05 ± 20.75
n	277	555	555	554	555	554	555	554	4159
Height, cm									
Mean ± SD	169.11 ± 9.84	168.66 ± 10.19	169.34 ± 10.79	169.48 ± 10.27	169.32 ± 10.79	168.56 ± 10.18	170.20 ± 10.33	169.25 ± 10.48	169.30 ± 10.40
n	277	555	554	554	555	554	555	554	4158
Body mass index, kg/m^2									
Mean ± SD	32.57 ± 6.05	31.93 ± 6.27	32.04 ± 5.95	32.03 ± 6.46	32.12 ± 6.30	32.04 ± 6.33	31.75 ± 6.02	32.05 ± 6.05	32.03 ± 6.19
n	277	555	554	554	555	554	555	554	4158
Participation in substudy, n (%)									
Yes	52 (18.8)	108 (19.5)	109 (19.6)	110 (19.9)	106 (19.1)	109 (19.7)	104 (18.7)	107 (19.3)	805 (19.4)
No	225 (81.2)	447 (80.5)	446 (80.4)	444 (80.1)	449 (80.9)	445 (80.3)	451 (81.3)	447 (80.7)	3354 (80.6)

(Applicant table: csr table 11.2.1-1, page 103)

Disease characteristics such as the status of hypertension (newly diagnosed vs. previously diagnosed), duration of known hypertension, pre-study treatment status, and stage of essential hypertension were also similar for patients in the different treatment groups. The mean duration of hypertension was 7.7 years. Most patients had been previously diagnosed with hypertension (95.4%), were currently being treated (79.4%), and had stage 2 essential hypertension (62.3%) at randomization (as assessed by DBP ≥ 100 mm Hg and/or SBP ≥ 160 mm Hg following the single-blind placebo washout/run-in period). These data are shown in the following table.

Table 5: History of hypertension

Parameter	*Placebo (N = 277)*	*FDC 10/160 (N = 555)*	*FDC 10/320 (N = 555)*	*FDC 20/320 (N = 554)*	*NEB 10 (N = 555)*	*NEB 40 (N = 554)*	*VAL 160 (N = 555)*	*VAL 320 (N = 554)*	*Total (N = 4159)*
Hypertension diagnosed, n (%)									
Newly diagnosed?	13 (4.7)	23 (4.1)	31 (5.6)	32 (5.8)	22 (4.0)	22 (4.0)	29 (5.2)	19 (3.4)	191 (4.6)
Previously diagnosed?	264 (95.3)	532 (95.9)	524 (94.4)	522 (94.2)	533 (96.0)	532 (96.0)	526 (94.8)	535 (96.6)	3968 (95.4)
Currently being treated, n (%)[a]									
Yes	212 (80.3)	429 (80.6)	420 (80.2)	402 (77.0)	408 (76.5)	432 (81.2)	420 (79.8)	427 (79.8)	3150 (79.4)
No	52 (19.7)	103 (19.4)	104 (19.8)	120 (23.0)	125 (23.5)	100 (18.8)	106 (20.2)	108 (20.2)	818 (20.6)
Duration of hypertension, years									
Mean ± SD	7.8 ± 8.1	7.5 ± 7.7	7.5 ± 7.6	7.6 ± 7.6	7.8 ± 8.3	7.8 ± 7.9	7.8 ± 7.7	7.6 ± 7.7	7.7 ± 7.8
n	277	555	555	554	555	554	555	554	4159
Essential hypertension stage[b], n (%)									
Stage 1	185 (66.8)	366 (65.9)	374 (67.4)	344 (62.1)	386 (69.5)	352 (63.5)	362 (65.2)	350 (63.2)	2719 (65.4)
Stage 2	92 (33.2)	189 (34.1)	181 (32.6)	210 (37.9)	169 (30.5)	202 (36.5)	193 (34.8)	204 (36.8)	1440 (34.6)
Essential hypertension stage[c], n (%)									
Stage 1	103 (37.2)	224 (40.4)	206 (37.1)	215 (38.8)	206 (37.1)	195 (35.2)	203 (36.6)	217 (39.2)	1569 (37.7)
Stage 2	174 (62.8)	331 (59.6)	349 (62.9)	339 (61.2)	349 (62.9)	359 (64.8)	352 (63.4)	337 (60.8)	2590 (62.3)

(Applicant table: csr 11.2.2.1-1, page 106)
a: Percentages are relative to the number of patients who were previously diagnosed.
b: Essential hypertension stage ascertained by the Investigator at the Screening Visit.
c: Essential hypertension stage ascertained by patient's blood pressure after the single-blind placebo washout period (post-hoc).

Prior medication use by therapeutic drug class and concomitant medication were generally similar among the treatment groups as shown in the following table.

Table 6: Prior medications with frequencies ≥ 10%

Therapeutic Drug Class[a] *Drug Name*[b]	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 554) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 554) n (%)*	*Total (N = 4159) n (%)*
Any medication	**247 (89.2)**	**489 (88.1)**	**490 (88.3)**	**484 (87.4)**	**495 (89.2)**	**504 (91.0)**	**489 (88.1)**	**496 (89.5)**	**3694 (88.8)**
ACE inhibitors, plain	91 (32.9)	194 (35.0)	203 (36.6)	208 (37.5)	159 (28.6)	208 (37.5)	201 (36.2)	179 (32.3)	1443 (34.7)
Lisinopril	70 (25.3)	143 (25.8)	152 (27.4)	157 (28.3)	124 (22.3)	157 (28.3)	159 (28.6)	138 (24.9)	1100 (26.4)
HMG CoA reductase inhibitors	48 (17.8)	112 (20.2)	111 (20.0)	112 (20.2)	111 (20.0)	121 (21.8)	115 (20.7)	111 (20.0)	841 (20.2)
Simvastatin	29 (10.5)	47 (8.5)	41 (7.4)	48 (8.7)	45 (8.1)	53 (9.6)	57 (10.3)	50 (9.0)	370 (8.9)
β-blocking agents, selective	43 (15.5)	95 (17.1)	101 (18.2)	75 (13.5)	87 (15.7)	77 (13.9)	92 (16.6)	94 (17.0)	664 (16.0)
Platelet aggregation inhibitors excluding heparin	42 (15.2)	83 (15.0)	80 (14.4)	68 (12.3)	82 (14.8)	92 (16.6)	86 (15.5)	80 (14.4)	613 (14.7)
Acetylsalicylic acid	42 (15.2)	81 (14.6)	79 (14.2)	68 (12.3)	82 (14.8)	92 (16.6)	84 (15.1)	79 (14.3)	607 (14.6)
Thiazides, plain	41 (14.8)	80 (14.4)	78 (14.1)	82 (14.8)	70 (12.6)	78 (14.1)	70 (12.6)	80 (14.4)	579 (13.9)
Hydrochlorothiazide	41 (14.8)	80 (14.4)	78 (14.1)	82 (14.8)	70 (12.6)	78 (14.1)	70 (12.6)	80 (14.4)	579 (13.9)
Propionic acid derivatives	43 (15.5)	66 (11.9)	74 (13.3)	82 (14.8)	67 (12.1)	60 (10.8)	81 (14.6)	89 (16.1)	562 (13.5)
Ibuprofen	30 (10.8)	48 (8.6)	58 (10.5)	65 (11.7)	50 (9.0)	46 (8.3)	58 (10.5)	60 (10.8)	415 (10.0)
Dihydropyridine derivatives	30 (10.8)	60 (10.8)	69 (12.4)	57 (10.3)	59 (10.6)	59 (10.6)	61 (11.0)	66 (11.9)	461 (11.1)
Biguanides	28 (10.1)	54 (9.7)	68 (12.3)	55 (9.9)	54 (9.7)	67 (12.1)	65 (11.7)	58 (10.5)	449 (10.8)
Metformin	24 (8.7)	50 (9.0)	63 (11.4)	51 (9.2)	49 (8.8)	64 (11.6)	58 (10.5)	55 (9.9)	414 (10.0)
Angiotensin II antagonists, plain	25 (9.0)	74 (13.3)	42 (7.6)	50 (9.0)	67 (12.1)	54 (9.7)	59 (10.6)	62 (11.2)	433 (10.4)
Proton pump inhibitors	27 (9.7)	48 (8.6)	64 (11.5)	51 (9.2)	61 (11.0)	53 (9.6)	54 (9.7)	70 (12.6)	428 (10.3)
Multivitamins, plain	35 (12.6)	43 (7.7)	43 (7.7)	57 (10.3)	56 (10.1)	53 (9.6)	58 (10.5)	49 (8.8)	394 (9.5)
Multivitamins, plain	35 (12.6)	41 (7.4)	43 (7.7)	54 (9.7)	54 (9.7)	50 (9.0)	56 (10.1)	48 (8.7)	381 (9.2)
Anilides	23 (8.3)	51 (9.2)	48 (8.6)	60 (10.8)	56 (10.1)	38 (6.9)	45 (8.1)	44 (7.9)	365 (8.8)

(Applicant table: csr table 11.2.4-1 page 117)

Baseline values for the efficacy assessments (mean seated trough DBP/SBP, mean seated pulse rate, mean standing DBP/SBP) are shown for the ITT Population in the following table. Baseline values for all efficacy assessments were similar and well-balanced among the treatment groups.

Table 7: Baseline efficacy variable

Efficacy Parameter, Unit	*Placebo (N = 277)*	*FDC 10/160 (N = 549)*	*FDC 10/320 (N = 548)*	*FDC 20/320 (N = 550)*	*NEB 10 (N = 552)*	*NEB 40 (N = 547)*	*VAL 160 (N = 548)*	*VAL 320 (N = 547)*	*Total (N = 4118)*
Seated trough DBP, mm Hg									
Mean ± SD	99.8 ± 3.5	99.6 ± 3.5	99.6 ± 3.5	99.9 ± 3.7	99.9 ± 3.5	99.8 ± 3.6	99.8 ± 3.8	99.7 ± 3.6	99.8 ± 3.6
n	277	549	548	550	552	547	548	547	4118
Seated trough SBP, mm Hg									
Mean ± SD	155.4 ± 11.2	154.6 ± 11.8	155.4 ± 11.1	154.6 ± 11.5	155.1 ± 11.8	155.1 ± 11.6	155.8 ± 12.1	155.1 ± 11.7	155.1 ± 11.6
n	277	549	548	550	552	547	548	547	4118
Seated pulse rate, bpm									
Mean ± SD	78.0 ± 10.7	77.8 ± 11.0	77.3 ± 10.7	78.2 ± 10.8	77.0 ± 10.7	77.6 ± 10.8	77.5 ± 10.7	77.1 ± 11.4	77.5 ± 10.9
n	277	549	548	550	552	547	548	547	4118
Standing DBP, mm Hg									
Mean ± SD	101.5 ± 7.4	101.9 ± 7.9	101.1 ± 7.7	101.7 ± 7.4	101.4 ± 7.3	101.1 ± 7.5	101.7 ± 7.4	101.2 ± 7.3	101.4 ± 7.5
n	270	535	531	535	536	538	542	532	4019
Standing SBP, mm Hg									
Mean ± SD	157.2 ± 15.8	156.4 ± 15.7	156.0 ± 14.3	155.8 ± 14.5	156.5 ± 14.8	156.5 ± 14.8	156.7 ± 15.7	155.9 ± 15.0	156.3 ± 15.1
n	270	535	531	535	536	538	542	532	4019

(Appicant table: csr table 11.2.3-1, page 112)

Baseline efficacy variables for patients who participated in the 24-hour ABPM substudy are shown by treatment group in the following table. Baseline efficacy values for patients who participated in this substudy were similar to the overall baseline efficacy values for the ITT Population.

Table 8: Baseline efficacy variables for patients who participated in the Substudy

Efficacy Parameter, Unit	*Placebo (N1 = 52)*	*FDC 10/160 (N1 = 107)*	*FDC 10/320 (N1 = 108)*	*FDC 20/320 (N1 = 110)*	*NEB 10 (N1 = 105)*	*NEB 40 (N1 = 107)*	*VAL 160 (N1 = 103)*	*VAL 320 (N1 = 105)*	*Total (N1 = 797)*
Seated trough DBP, mm Hg									
Mean ± SD	99.6 ± 3.3	99.6 ± 3.5	100.3 ± 3.6	99.9 ± 3.7	99.8 ± 3.6	99.7 ± 3.6	100.0 ± 3.9	100.5 ± 4.1	100.0 ± 3.7
n	52	107	108	110	105	107	103	105	797
Seated trough SBP, mm Hg									
Mean ± SD	155.3 ± 10.1	156.9 ± 12.3	158.0 ± 10.4	154.6 ± 11.1	153.9 ± 12.2	157.2 ± 12.0	158.3 ± 11.7	155.2 ± 11.3	156.2 ± 11.5
n	52	107	108	110	105	107	103	105	797
Seated pulse rate, bpm									
Mean ± SD	77.7 ± 10.4	77.3 ± 10.9	77.2 ± 11.8	79.5 ± 10.2	77.9 ± 12.7	76.2 ± 10.1	77.5 ± 12.1	78.2 ± 13.4	77.7 ± 11.5
n	52	107	108	110	105	107	103	105	797
Standing DBP, mm Hg									
Mean ± SD	101.7 ± 6.2	102.6 ± 8.2	102.2 ± 7.3	102.1 ± 7.8	101.7 ± 6.9	100.6 ± 7.9	103.0 ± 7.8	102.7 ± 8.4	102.1 ± 7.7
n	51	104	105	109	104	105	101	104	783
Standing SBP, mm Hg									
Mean ± SD	156.2 ± 13.5	160.5 ± 16.5	159.3 ± 13.8	157.3 ± 14.4	155.1 ± 14.7	158.8 ± 15.8	162.0 ± 15.0	156.4 ± 14.7	158.3 ± 15.0
n	51	104	105	109	104	105	101	104	783
Mean 24-hour ambulatory DBP, mm Hg									
Mean ± SD	87.4 ± 9.9	87.9 ± 9.2	88.1 ± 8.6	86.9 ± 9.2	86.9 ± 8.4	87.3 ± 9.6	87.5 ± 9.5	88.9 ± 9.4	87.6 ± 9.2
n	52	101	106	110	104	103	103	103	782
Mean 24-hour ambulatory SBP, mm Hg									
Mean ± SD	138.9 ± 13.9	143.1 ± 14.1	141.8 ± 12.9	140.8 ± 13.5	139.2 ± 10.8	142.5 ± 14.3	142.5 ± 14.4	141.6 ± 12.9	141.5 ± 13.4
n	52	101	106	110	104	103	103	103	782
Mean daytime (6 AM-10 PM) ambulatory DBP, mm Hg									
Mean ± SD	90.8 ± 10.2	91.0 ± 9.6	91.5 ± 9.0	90.4 ± 9.8	90.3 ± 9.0	90.7 ± 9.8	90.7 ± 10.3	92.2 ± 9.6	91.0 ± 9.6
n	52	101	106	110	104	103	103	103	782
Mean daytime (6 AM-10 PM) ambulatory SBP, mm Hg									
Mean ± SD	142.7 ± 14.2	146.8 ± 14.2	146.0 ± 13.2	145.0 ± 14.0	143.3 ± 11.5	146.8 ± 14.5	146.5 ± 15.5	145.6 ± 13.2	145.5 ± 13.8
n	52	101	106	110	104	103	103	103	782
Mean nighttime (10 PM-6 AM) ambulatory DBP, mm Hg									
Mean ± SD	79.1 ± 11.2	80.2 ± 10.8	79.7 ± 9.8	78.4 ± 10.7	78.5 ± 10.0	79.0 ± 10.7	79.6 ± 10.4	80.6 ± 10.8	79.4 ± 10.5
n	52	101	106	110	104	103	103	103	782
Mean nighttime (10 PM-6 AM) ambulatory SBP, mm Hg									
Mean ± SD	129.7 ± 16.0	133.9 ± 16.5	131.7 ± 14.6	130.4 ± 15.5	129.1 ± 12.3	132.3 ± 15.9	132.6 ± 14.9	131.9 ± 14.6	131.5 ± 15.0
n	52	101	106	110	104	103	103	103	782

(Applicant table: csr table 11.2.3-2, page 114)

Reviewer comments: In the pivotal trial, demographic and key baseline characteristics were generally well-balanced across the treatment groups.

6.1.3 Subject Disposition

A total of 13,250 patients were screened for eligibility in the pivotal trial; 4161 patients were randomized to receive double-blind treatment; 4159 patients received at least 1 dose of treatment; 1664 patients received nebivolol/valsartan FDC (555 patients received FDC 5/80 mg

and then FDC 10/160 mg for 4 weeks each, 555 patients received FDC 5/160 mg and then FDC 10/320 mg, and 554 patients received FDC 10/160 mg and then FDC 20/320 mg) during the 8-week double blind treatment period. As well, 555 patients received nebivolol 5 mg followed by nebivolol 10 mg, and 554 received nebivolol 20 mg followed by nebivolol 40 mg; 555 patients received valsartan 80 mg followed by valsartan 160 mg, and 554 received valsartan 160 mg followed by valsartan 320 mg.

The reasons for prematurely discontinuing from the double-blind treatment period are summarized in the table below. Approximately 10% of subjects prematurely discontinued from the double-blind treatment period. The percentage of subjects discontinuing therapy prematurely was highest in the nebivolol 40 mg arm and lowest in the FDC 20/320 arm (13.7% and 8.7%, respectively). Compared with the other mono and combo therapy arms, more subjects in the nebivolol 40 mg arm discontinued therapy prematurely because of an AE or seated pulse < 50 bpm. As might be expected, discontinuations due to insufficient therapeutic response were more common in the placebo group than in the treatment groups. Otherwise, discontinuation rates and reasons for discontinuation were, for the most part, similar between the placebo and treatment groups and between the monotherapies and the combination therapy.

Table 9: Number (%) of patients discontinued from the Study during the double-blind treatment period

Patient Status	*Placebo (N = 277) n (%)*	*FDC 10/160 (N = 555) n (%)*	*FDC 10/320 (N = 555) n (%)*	*FDC 20/320 (N = 554) n (%)*	*NEB 10 (N = 555) n (%)*	*NEB 40 (N = 555) n (%)*	*VAL 160 (N = 555) n (%)*	*VAL 320 (N = 555) n (%)*	*Total (N = 4161) n (%)*
Completed DBTP	244 (88.1)	490 (88.3)	496 (89.4)	506 (91.3)	505 (91.0)	479 (86.3)	498 (89.7)	497 (89.5)	3715 (89.3)
Prematurely discontinued from DBTP	33 (11.9)	65 (11.7)	59 (10.6)	48 (8.7)	50 (9.0)	76 (13.7)	57 (10.3)	58 (10.5)	446 (10.7)
AE	10 (3.6)	15 (2.7)	9 (1.6)	9 (1.6)	12 (2.2)	22 (4.0)	10 (1.8)	10 (1.8)	97 (2.3)
Insufficient therapeutic response	9 (3.2)	6 (1.1)	5 (0.9)	3 (0.5)	6 (1.1)	1 (0.2)	12 (2.2)	7 (1.3)	49 (1.2)
Protocol deviation/ violation	2 (0.7)	12 (2.2)	4 (0.7)	6 (1.1)	4 (0.7)	11 (2.0)	6 (1.1)	11 (2.0)	56 (1.3)
Withdrawal of consent	5 (1.8)	22 (4.0)	20 (3.6)	12 (3.6)	12 (2.2)	18 (3.2)	13 (2.3)	17 (3.1)	119 (2.9)
Lost to follow-up	5 (1.8)	5 (0.9)	13 (2.3)	9 (1.6)	9 (1.6)	11 (2.0)	9 (1.6)	9 (1.6)	70 (1.7)
Seated pulse < 50 bpm	0	0	1 (0.2)	3 (0.5)	0	7 (1.3)	0	0	11 (0.3)
Low blood pressure (seated SBP < 100 or DBP < 60)	0	0	1 (0.2)	0	0	0	0	0	1 (0.0)
Other reasons	2 (0.7)	5 (0.9)	6 (1.1)	6 (1.1)	7 (1.3)	6 (1.1)	7 (1.3)	4 (0.7)	43 (1.0)

(Applicant table: csr table 10.1-1, page 93)

Reviewer comments: The percentage of subjects discontinuing from therapy was similar to what was seen in other combination product studies conducted in recent years, such as those for aliskiren and ARBs.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the difference in trough mean seated DBP reductions between the FDC treatment groups and each of the corresponding monotherapy treatment groups. The primary efficacy endpoint comparisons, as prespecified, were the difference in reduction in trough mean seated DBP between the FDC 20/320 mg treatment group and nebivolol 40 mg treatment group and between the FDC 20/320 mg treatment group and valsartan 320 mg treatment group.

The differences in reduction in trough mean seated DBP between the FDC 20/320 mg and the nebivolol 40 mg and valsartan 320 mg monotherapy treatment groups were statistically significant in the LOCF analysis. The LSMD (least squares mean difference) was –1.2 mmHg ($p = 0.03$; 95% CI of -0.1 to -2.3) for the comparison with nebivolol 40 mg and –4.4 mmHg ($p < 0.0001$; 95% CI of -3.3, -5.4) for the comparison with valsartan 320 mg. The other FDC treatment groups also showed statistically significantly greater reductions in DBP than their corresponding monotherapies as shown in the following table.

Table 10: Primary efficacy parameter: Change from baseline in trough seated DBP (mm Hg) at Week 8

Treatment Group	*n*	*LSM Change From Baseline (SE)*
Placebo	277	–7.1 (0.6)
Nebivolol 10 mg	552	–12.8 (0.4)
Nebivolol 40 mg	547	–14.5 (0.4)
Valsartan 160 mg	548	–10.9 (0.4)
Valsartan 320 mg	547	–11.4 (0.4)
FDC 10/160 mg	549	–15.0 (0.4)
FDC 10/320 mg	548	–15.1 (0.4)
FDC 20/320 mg	550	–15.7 (0.4)

Pairwise Comparison	*LSM Difference in Change From Baseline*	*95% CI for LSM Difference*	*p-Value*
Neb 10 mg vs placebo	–5.7	(–7.4, –4.4)	< 0.0001
Neb 40 mg vs placebo	–7.5	(–8.8, –6.1)	< 0.0001
Val 160 mg vs placebo	–3.9	(–5.2, –2.5)	< 0.0001
Val 320 mg vs placebo	–4.3	(–5.7, –3.0)	< 0.0001
FDC 10/160 mg vs placebo	–7.9	(–9.3, –6.6)	< 0.0001
FDC 10/320 mg vs placebo	–8.1	(–9.4, –6.7)	< 0.0001
FDC 20/320 mg vs placebo	–8.7	(–10.0, –7.3)	< 0.0001
FDC 10/160 mg vs Neb 10 mg	–2.2	(–3.3, –1.1)	< 0.0001
FDC 10/160 mg vs Val 160 mg	–4.1	(–5.1, –3.0)	< 0.0001
FDC 10/320 mg vs Neb 10 mg	–2.4	(–3.4, –1.3)	< 0.0001
FDC 10/320 mg vs Val 320 mg	–3.7	(–4.8, –2.6)	< 0.0001
FDC 20/320 mg vs Neb 40 mg[a]	–1.2	(–2.3, –0.1)	0.03
FDC 20/320 mg vs Val 320 mg[a]	–4.4	(–5.4, –3.3)	< 0.0001

(Applicant table: csr table 11.4.1.1-1, page 123)

Reviewer comments: Although the reduction in DBP with the highest FDC dose (20/320 mg) was statistically greater than the reductions in DBP observed with the highest approved doses of the monotherapies, the mean difference in the change from baseline in DBP for the highest FDC dose versus the highest approved dose of nebivolol (40 mg) was small- only 1.2 mmHg. An effect of this size may not be clinically meaningful.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary efficacy parameters included the change from baseline in trough mean seated SBP at Week 8, the change from baseline in trough mean seated DBP and SBP at Week 4, the change in mean 24-hour ambulatory DBP and SBP from baseline to Week 8, and the proportion of patients achieving a specified BP treatment goal at Week 8.

*Change From Baseline in Seated Trough Systolic Blood Pressure at Week 8***:** The differences in reduction in trough mean seated SBP between the FDC 20/320 mg group and the nebivolol 40 mg and valsartan 320 mg monotherapy groups were statistically significant in the LOCF analysis (LSMD of –2.9 mmHg, p = 0.0013 for nebivolol and -3.1 mmHg, p=0.0005 for valsartan). The other FDC groups also showed a greater reduction in SBP than each corresponding monotherapy group. Data are summarized in the following table.

Table 11: Change from baseline in trough seated systolic blood pressure (mm Hg) at Week 8

Treatment Group	*n*	*LSM Change From Baseline (SE)*	
Placebo	277	–7.2 (0.9)	
Nebivolol 10 mg	552	–13.4 (0.7)	
Nebivolol 40 mg	547	–14.2 (0.7)	
Valsartan 160 mg	548	–13.1 (0.7)	
Valsartan 320 mg	547	–14.0 (0.7)	
FDC 10/160 mg	549	–17.0 (0.7)	
FDC 10/320 mg	548	–17.0 (0.7)	
FDC 20/320 mg	550	–17.1 (0.7)	
Pairwise Comparison	*LSM Difference in Change From Baseline*	*95% CI for LSM Difference*	*p-Value*
Neb 10 mg vs placebo	–6.2	(–8.3, –4.0)	< 0.0001
Neb 40 mg vs placebo	–7.0	(–9.2, –4.8)	< 0.0001
Val 160 mg vs placebo	–5.9	(–8.0, –3.7)	< 0.0001
Val 320 mg vs placebo	–6.8	(–8.9, –4.6)	< 0.0001
FDC 10/160 mg vs placebo	–9.8	(–11.9, –7.6)	< 0.0001
FDC 10/320 mg vs placebo	–9.7	(–11.9, –7.6)	< 0.0001
FDC 20/320 mg vs placebo	–9.9	(–12.1, –7.7)	< 0.0001
FDC 10/160 mg vs Neb 10 mg	–3.6	(–5.4, –1.8)	< 0.0001
FDC 10/160 mg vs Val 160 mg	–3.9	(–5.7, –2.1)	< 0.0001
FDC 10/320 mg vs Neb 10 mg	–3.6	(–5.3, –1.8)	< 0.0001
FDC 10/320 mg vs Val 320 mg	–3.0	(–4.7, –1.2)	0.0011
FDC 20/320 mg vs Neb 40 mg	–2.9	(–4.7, –1.1)	0.0013
FDC 20/320 mg vs Val 320 mg	–3.1	(–4.9, –1.4)	0.0005

(Applicant table: csr table 11.4.1.2.1-1, page 126)

Change from Baseline in Seated Trough Blood Pressure at Week 4: Three FDC doses including FDC 5/80, 5/160 and 10/160 mg were evaluated at week 4. At week 4, the two lower FDC doses (5/80 and 5/160 mg) showed a statistically significantly greater reduction in both DBP and SBP

than each of corresponding monotherapies with the exception of the FDC 5/160 mg dose vs valsartan 160 mg dose for SBP (LSMD = –1.4 mm Hg, p = 0.1097). Data are summarized in the following tables.

Table 12: Change from baseline in trough seated diastolic blood pressure at Week 4

Treatment Group	***n***	***LSM Change From Baseline (SE)***	
Placebo	277	–6.4 (0.5)	
Nebivolol 5 mg	552	–10.8 (0.4)	
Nebivolol 20 mg	547	–13.8 (0.4)	
Valsartan 80 mg	548	–10.2 (0.4)	
Valsartan 160 mg	547	–10.9 (0.4)	
FDC 5/80 mg	549	–13.5 (0.4)	
FDC 5/160 mg	548	–13.8 (0.4)	
FDC 10/160 mg	550	–14.3 (0.4)	
Pairwise Comparison	***LSM Difference in Change From Baseline***	***95% CI for LSM Difference***	***p-Value***
Neb 5 mg vs placebo	–4.4	(–5.7, –3.2)	< 0.0001
Neb 20 mg vs placebo	–7.5	(–8.7, –6.2)	< 0.0001
Val 80 mg vs placebo	–3.9	(–5.1, –2.6)	< 0.0001
Val 160 mg vs placebo	–4.6	(–5.8, –3.3)	< 0.0001
FDC 5/80 mg vs placebo	–7.2	(–8.4, –5.9)	< 0.0001
FDC 5/160 mg vs placebo	–7.4	(–8.7, –6.1)	< 0.0001
FDC 10/160 mg vs placebo	–7.9	(–9.2, –6.6)	< 0.0001
FDC 5/80 mg vs Neb 5 mg	–2.7	(–3.8, –1.7)	< 0.0001
FDC 5/80 mg vs Val 80 mg	–3.3	(–4.4, –2.3)	< 0.0001
FDC 5/160 mg vs Neb 5 mg	–3.0	(–4.0, –1.9)	< 0.0001
FDC 5/160 mg vs Val 160 mg	–2.9	(–3.9, –1.8)	< 0.0001

(Applicant table: csr table 11.4.1.2.2.1-1, page 128)

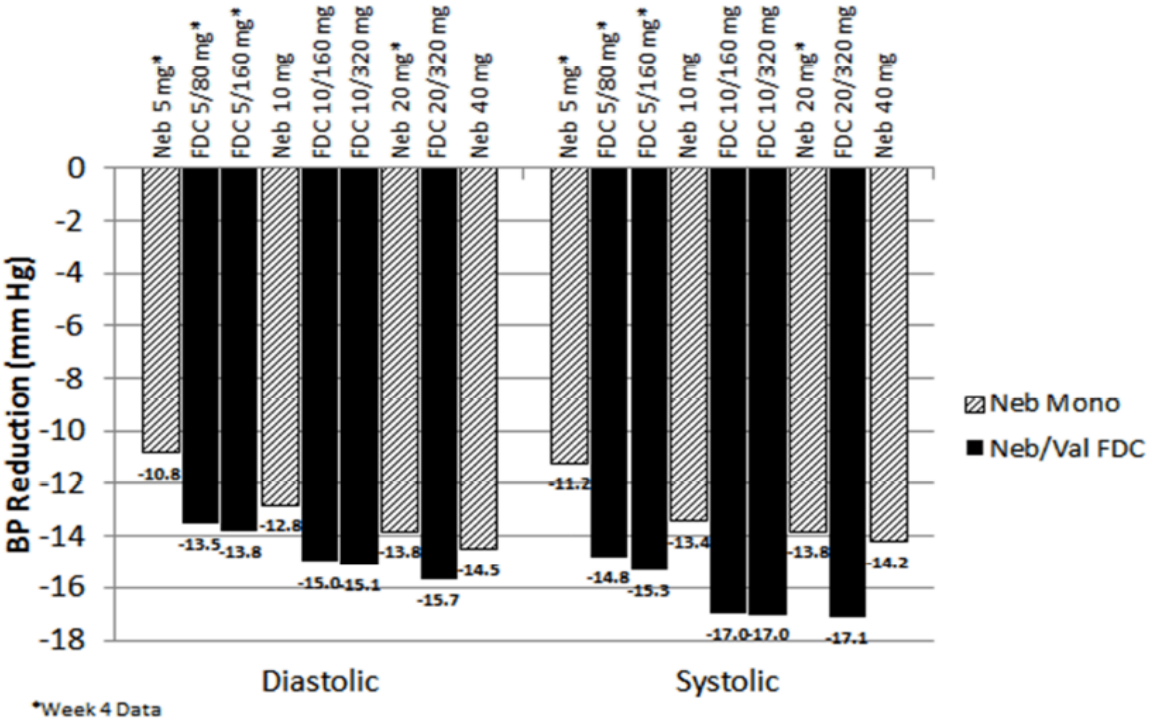
Table 13: Change from baseline in trough seated systolic blood pressure at Week 4

Treatment Group	***n***	***LSM Change From Baseline (SE)***	
Placebo	277	–6.5 (0.9)	
Nebivolol 5 mg	552	–11.2 (0.6)	
Nebivolol 20 mg	547	–13.8 (0.6)	
Valsartan 80 mg	548	–11.9 (0.6)	
Valsartan 160 mg	547	–13.9 (0.6)	
FDC 5/80 mg	549	–14.8 (0.6)	
FDC 5/160 mg	548	–15.3 (0.6)	
FDC 10/160 mg	550	–15.5 (0.6)	
Pairwise Comparison	***LSM Difference in Change From Baseline***	***95% CI for LSM Difference***	***p-Value***
Neb 5 mg vs placebo	–4.7	(–6.7, –2.7)	< 0.0001
Neb 20 mg vs placebo	–7.4	(–9.4, –5.4)	< 0.0001
Val 80 mg vs placebo	–5.4	(–7.4, –3.4)	< 0.0001
Val 160 mg vs placebo	–7.5	(–9.5, –5.4)	< 0.0001
FDC 5/80 mg vs placebo	–8.3	(–10.3, –6.3)	< 0.0001
FDC 5/160 mg vs placebo	–8.8	(–10.9, –6.8)	< 0.0001
FDC 10/160 mg vs placebo	–9.0	(–11.0, –7.0)	< 0.0001
FDC 5/80 mg vs Neb 5 mg	–3.6	(–5.3, –1.9)	< 0.0001
FDC 5/80 mg vs Val 80 mg	–2.9	(–4.5, –1.2)	0.0007
FDC 5/160 mg vs Neb 5 mg	–4.1	(–5.8, –2.5)	< 0.0001
FDC 5/160 mg vs Val 160 mg	–1.4	(–3.0, –0.3)	0.1097

(Applicant table: csr table 11.4.1.2.2.1-2, page 129)

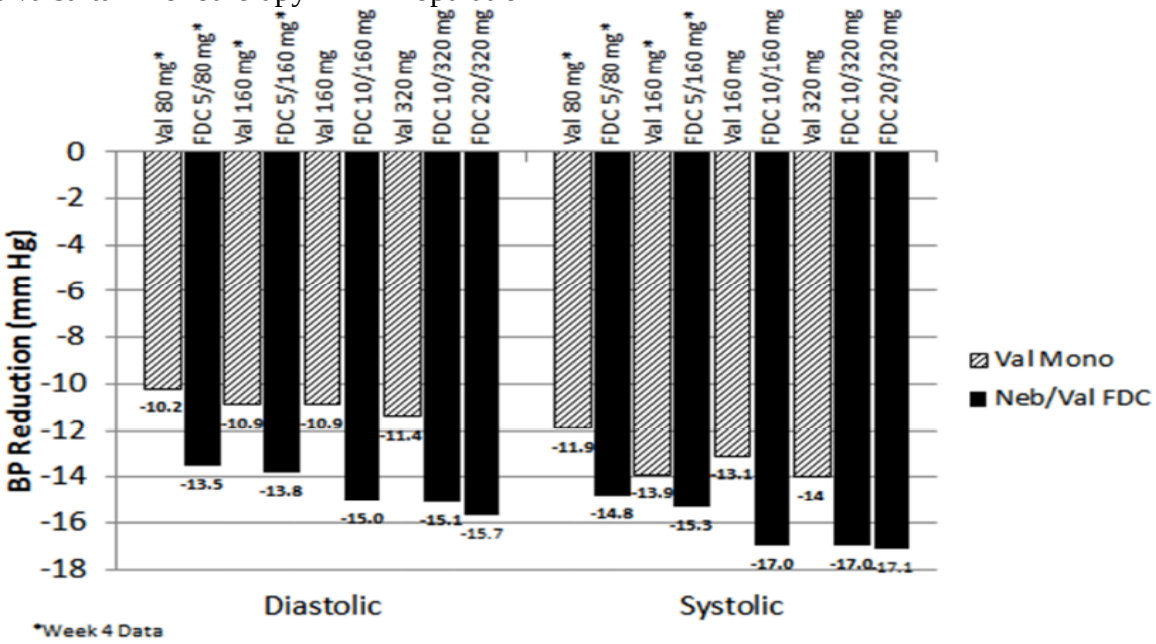
The following figures summarize the mean DBP and SBP reductions from baseline for all FDCs (5/80 mg, 5/160 mg, 10/160 mg, 10/320 mg, and 20/320 mg), nebivolol monotherapies (5 mg, 10 mg, 20 mg, and 40 mg), and valsartan monotherapies (80 mg, 160 mg, and 320 mg). DBP and SBP reductions from baseline are denoted directly below each bar. As shown in the figure, the difference in DBP reduction between FDC 20/320 mg and Nebivolol 40 mg was very small. In addition, there was no significant dose-response relationship in the monotherapy or FDC groups (see also Section 6.1.8, Analysis of Clinical Information Relevant to Dosing Recommendations).

Figure 3: Blood pressure reductions from baseline by treatment group for FDC treatment Groups versus nebivolol monotherapy—ITT Population



(Applicant figure: Summary of clinical efficacy figure 3.2.3.2-1, page 43)

Figure 4: Blood pressure reductions from baseline by treatment group for FDC treatment groups versus valsartan monotherapy—ITT Population



(Applicant figure: Summary of clinical efficacy figure 3.2.3.1-1, page 42)

The following table compares sample sizes and efficacy findings for some recently approved combination antihypertensive products with the nebivolol/valsartan FDC at the highest dose level. Relative to these other products, the nebivolol/valsartan FDC has a smaller effect size in the pairwise comparison.

Table 14: Comparison of efficacy between nebivolol/valsartan and other recently approved combination products at the highest dose level

Combination products	Pairwise comparison (mg)	Number of subjects	msDBP (mmHg)		msSBP (mmHg)	
			LSM difference	95% CI	LSM difference	95% CI
Nebivolol / Valsartan	FDC 20/320 vs Nebivolol 40	**550 vs 547**	**-1.2**	-2.3, -0.1	-2.9	-4.7, -1.1
	FDC 20/320 vs Valsartan 320	550 vs 547	-4.4	-5.4, -3.3	-3.1	-4.9, -1.4
Aliskiren/ valsartan	FDC 300/320 vs Aliskiren 300	438 vs 430	-3.2	-4.3, -2.0	-4.2	-6.1, -2.4
	FDC 300/320 vs Valsartan 320	438 vs 453	-2.5	-3.6, -1.4	-4.4	-6.3, -2.6
Valsartan/ amilodipine	FDC 320/10 vs valsartan 320	208 vs 207	-5.3	-6.9, -3.8	-8.5	-10.9, -6.2
	FDC 320/10 vs amilodipine 10	208 vs 206	-3.0	-4.6, -1.5	-4.3	-6.6, -1.9
Aliskiren/ amilodipine	FDC 300/10 vs Aliskiren 300	183 vs 201	-6.3	-7.2, -6.4	-7.8	-9.2, -6.4
	FDC 300/10 vs amilodipine 10	183vs 179	-2.7	-3.6, -1.8	-2.2	-3.7, -0.7
Aliskiren/ HCTZ	FDC 300/25 vs Aliskiren 300	173 vs 180	-4.0	-5.7, -2.3	-5.5	-8.1, -2.8
	FDC 300/25 vs HCTZ 25	173 vs 173	-4.9	-6.6, -3.2	-6.9	-9.6, -3.2

(Reviewer table)

Change in Mean 24-Hour Ambulatory Blood Pressure From Baseline to Week 8: According to the applicant's analyses, the reduction in mean 24-hour ambulatory diastolic and systolic pressure was statistically significantly greater in the FDC 20/320 mg group than in the valsartan 320 mg monotherapy group. In contrast, the reduction was not statistically significantly greater in the FDC 20/320 mg group than in the nebivolol 40 mg monotherapy group.

Table 15: Change in mean 24-hour ambulatory diastolic blood pressure from baseline to Week 8

Treatment Group	***n***	***LSM Change From Baseline (SE)***	
Placebo	39	0.5 (1.1)	
Nebivolol 40 mg	77	–10.7 (0.8)	
Valsartan 320 mg	82	–7.7 (0.8)	
FDC 20/320 mg	86	–12.3 (0.8)	
Pairwise Comparison	***LSM Difference in Change From Baseline***	***95% CI for LSM Difference***	***p-Value***
Neb 40 mg vs placebo	–11.2	(–13.8, –8.5)	< 0.0001
Val 320 mg vs placebo	–8.2	(–10.8, –5.5)	< 0.0001
FDC 20/320 mg vs placebo	–12.7	(–15.4, –10.1)	< 0.0001
FDC 20/320 mg vs Neb 40 mg	–1.6	(–3.7, 0.6)	0.1486
FDC 20/320 mg vs Val 320 mg	–4.6	(–6.6, –2.5)	< 0.0001

(Applicant table: csr table 11.4.1.2.2.2–1, page 130)

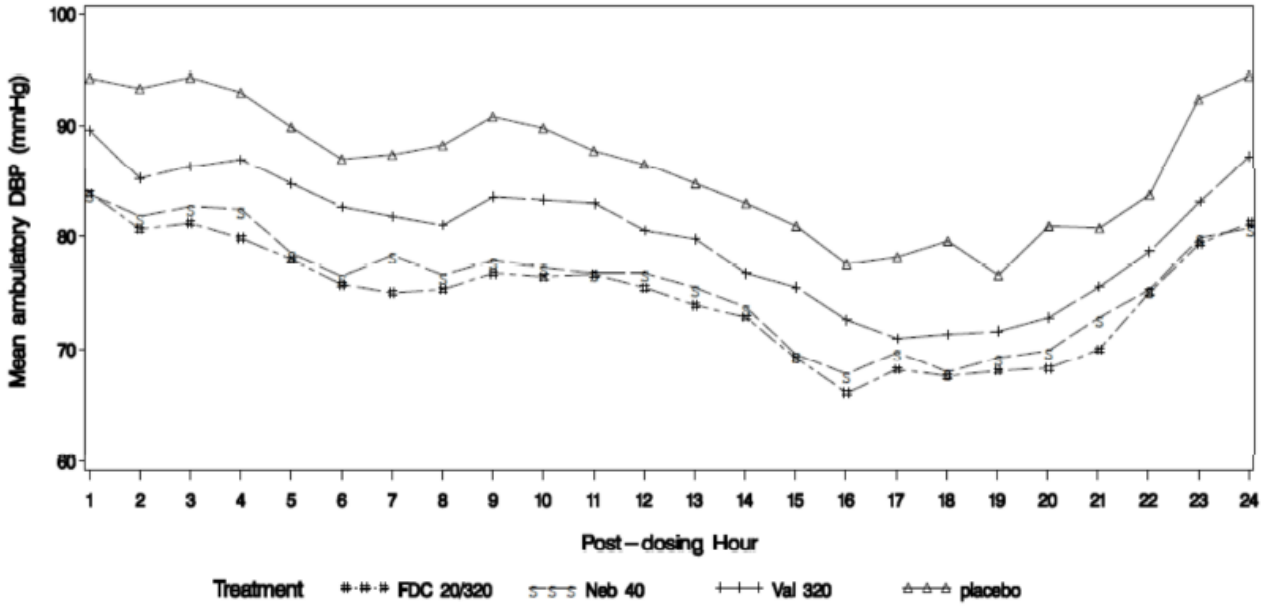
Table 16: Change in mean 24–hour ambulatory systolic blood pressure from baseline to Week 8

Treatment Group	***n***	***LSM Change From Baseline (SE)***	
Placebo	39	–0.5 (1.8)	
Nebivolol 40 mg	77	–14.2 (1.3)	
Valsartan 320 mg	82	–11.2 (1.3)	
FDC 20/320 mg	86	–16.3 (1.2)	
Pairwise Comparison	***LSM Difference in Change From Baseline***	***95% CI for LSM Difference***	***p-Value***
Neb 40 mg vs placebo	–13.7	(–17.9, –9.4)	< 0.0001
Val 320 mg vs placebo	–10.6	(–14.8, –6.4)	< 0.0001
FDC 20/320 mg vs placebo	–15.7	(–19.9, –11.6)	< 0.0001
FDC 20/320 mg vs Neb 40 mg	–2.1	(–5.4, 1.3)	0.2312
FDC 20/320 mg vs Val 320 mg	–5.1	(–8.4, –1.8)	0.0027

(Applicant table: csr table 11.4.1.2.2.2–2, page 131)

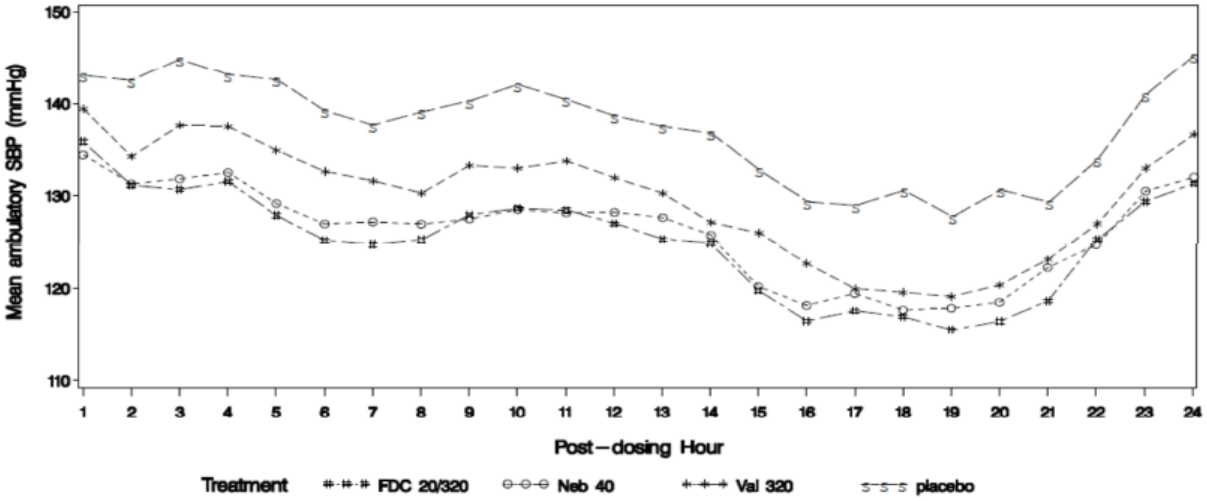
The figures below show the time course for changes in DBP and SBP in the placebo, FDC 20/320 mg, and each monotherapy at the highest dose. The curves for the FDC 20/320 mg and nebivolol 40 mg dose groups overlap, indicating a similar effect on blood pressure reduction in these two groups.

Figure 5: Changes in mean 24-hour ambulatory DBP by post-dosing hour for FDC 20/320 mg, Nebivolol 40 mg, and Valsartan 320 mg



(Applicant figure: csr figure 11.4.1.3.4–1, page 153)

Figure 6: Changes in mean 24-hour ambulatory SBP by post-dosing hour for FDC 20/320 mg, Nebivolol 40 mg, and Valsartan 320 mg



(Applicant figure: csr figure 11.4.1.3.4–2, page 155)

Blood pressure control: BP control was defined as a SBP < 140 mm Hg *and* DBP < 90 mm Hg for patients without type 2 diabetes, and a SBP < 130 mm Hg *and* DBP < 80 mm Hg for patients with type 2 diabetes.

Statistically significantly more patients receiving FDC 20/320 mg achieved BP control as compared with patients receiving nebivolol 40 mg, valsartan 320 mg, or placebo. Specifically, 51.8% of patients receiving FDC 20/320 mg reached the BP control goal, as compared with

45.2%, 35.6%, and 20.9% of patients receiving nebivolol 40 mg, valsartan 320 mg, and placebo, respectively. Similar results were also observed in other FDC dose groups in comparison with the corresponding monotherapy groups. Data are summarized in the following table.

Table 17: Percentage of patients at diastolic and systolic treatment goals by treatment group-ITT population

Time Point	*FDC Dose*	*FDC*		*Comparator Monotherapy*			
				Nebivolol		*Valsartan*	
		BP Control %	*p-Value*[a]	**BP Control %**	**p-Value**[b]	**BP Control %**	**p-Value**[c]
Week 4	5/80	42.4	< 0.0001	31.0	< 0.0001	32.8	0.0027
	5/160	41.4	< 0.0001	31.0	< 0.0001	31.8	0.0002
Week 8	10/160	48.8	< 0.0001	38.6	0.0005	36.5	0.0001
	10/320	46.7	< 0.0001	38.6	0.0013	35.6	< 0.0001
	20/320	51.8	< 0.0001	45.2	0.0231	35.6	< 0.0001

(Applicant table: summary of clinical efficacy table 3.2.8.1–1, page 51)
a:p-Value is based on a logistic regression model comparing the FDC dose versus placebo.
b:p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding nebivolol monotherapy
c:p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding valsartan monotherapy

A post hoc analysis also examined BP control using a single BP criterion (SBP of < 140 mm Hg *and* DBP < 90 mm Hg) without stratification for diabetes status. As shown in the following table, the percentages of patients achieving BP control were statistically significantly greater with each FDC dose as compared with the corresponding monotherapies and with placebo.

Table 18: Post-hoc analysis: Percentage of patients at diastolic and systolic treatment goals by treatment group

Time Point	*FDC Dose*	*FDC*		*Comparator Monotherapy*			
				Nebivolol		*Valsartan*	
		BP Control %	*p-Value*[a]	**BP Control %**	**p-Value**[b]	**BP Control %**	**p-Value**[c]
Week 4	5/80	45.7	< 0.0001	34.8	0.0003	35.9	0.0033
	5/160	46.5	< 0.0001	34.8	< 0.0001	36.2	0.0001
Week 8	10/160	52.1	< 0.0001	42.8	0.0025	39.4	0.0001
	10/320	52.2	< 0.0001	42.8	0.0006	40.4	< 0.0001
	20/320	55.3	< 0.0001	48.8	0.0397	40.4	< 0.0001

(Applicant table: summary of clinical efficacy table 3.2.8.2–1, page 52)
a: p-Value is based on a logistic regression model comparing the FDC dose versus placebo.
b: p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding nebivolol monotherapy.
c: p-Value is based on a logistic regression model comparing the FDC dose versus the corresponding valsartan monotherapy.

Reviewer comments: At the end of the 8-week study, the FDC groups showed statistically significantly greater reductions in SBP than each of the corresponding monotherapy dose groups. A higher percentage of subjects achieved blood pressure control in the FDC 20/320 mg dose group than in the nebivolol 40mg and valsartan 320mg monotherapy groups. However, for the important clinical parameter of ABPM, there was no difference between the FDC 20/320 mg and the nebivolol 40 mg monotherapy. Regarding the sample size for the 24-hour ABPM substudy, about 100 subjects were enrolled in each treatment group and about 80 subjects in each treatment group completed the study. The sample size appears to be similar to that used in other combination product development programs; however, in these programs, the BP reduction on ABPM with the combination was greater than with the monotherapies at the highest dose level. The available data suggest that if there is a difference in 24-hour ambulatory blood pressure between FDC 20/320 mg and nebivolol 40 mg, it is likely to be small.

6.1.6 Other Endpoints:
None.

6.1.7 Subpopulations
Pre-specified subgroup analyses included diabetes status, race, age group, BMI category, sex, and ethnicity; the applicant also performed analyses by stage of hypertension. These analyses assessed reductions in DBP and SBP for each FDC, as compared with monotherapies or placebo, at 8 weeks.

Diabetic Status: There were about 80 subjects with diabetes (15%) in each treatment group. In general, there appeared to be greater reductions in both DBP and SBP in the FDC groups in the pairwise comparisons between the FDC groups and the corresponding monotherapies. However, relative to the pairwise comparisons in subjects without diabetes, the reductions appeared to be smaller in the pairwise comparisons in subjects with diabetics. In addition, the point estimate for the pairwise comparison for FDC 20/320 mg vs. nebivolol 40 mg favored nebivolol.

Table 19: Subgroup analysis by diabetes status: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	Diabetes	*Non-diabetes*	*Diabetes*	*Non-diabetes*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–1.2	–2.2	–0.8	–3.9
FDC 10/160 mg vs Val 160 mg	–3.0	–4.2	–2.4	–3.7
FDC 10/320 mg vs Neb 10 mg	–0.1	–2.6	–2.0	–3.9
FDC 10/320 mg vs Val 320 mg	–1.8	–4.1	–0.8	–3.5
FDC 20/320 mg vs Neb 40 mg	1.4	–1.8	2.0	–3.6
FDC 20/320 mg vs Val 320 mg	–2.5	–4.8	2.7	–4.1

(Applicant table: csr table 11.4.1.5.1–2, page 170)

Race: The percentage of black patients in the ITT Population was 9.8%. There was no difference in blood pressure reduction between FDC 20/320 mg and nebivolol 40 mg in these patients as shown in the following table.

Table 20: Subgroup analysis by race: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	Black	*Non-Black*	*Black*	*Non-Black*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–0.6	–2.2	–1.5	–3.6
FDC 10/160 mg vs Val 160 mg	–4.1	–4.1	–6.1	–3.4
FDC 10/320 mg vs Neb 10 mg	–3.0	–2.1	–4.6	–3.5
FDC 10/320 mg vs Val 320 mg	–7.1	–3.4	–9.1	–2.5
FDC 20/320 mg vs Neb 40 mg	0.2	–1.4	–0.2	–3.0
FDC 20/320 mg vs Val 320 mg	–4.0	–4.5	–3.3	–3.0

(Applicant table: csr table 11.4.1.5.3–2, page 176)

Age group: Based on the applicant's table, FDC 20/320 did not produce a greater reduction in SBP in patients≥ 65 years old than its corresponding monotherapies. The applicant claims that this may be related to the small sample size (368 of 4118 patients ≥ 65 years, 8.9% of the ITT population) and the significant placebo effect on SBP reduction (-15.1 mmHg).

Table 21: Subgroup analysis by age group: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	< 65 years	*≥ 65 years*	*< 65 years*	*≥ 65 years*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–2.1	–2.2	–3.6	–1.2
FDC 10/160 mg vs Val 160 mg	–4.3	–1.4	–4.1	3.3
FDC 10/320 mg vs Neb 10 mg	–2.0	–4.0	–3.5	–4.5
FDC 10/320 mg vs Val 320 mg	–3.7	–4.1	–3.2	–1.8
FDC 20/320 mg vs Neb 40 mg	–1.1	–3.2	–3.0	1.2
FDC 20/320 mg vs Val 320 mg	–4.6	–4.1	–3.5	2.4

(Applicant table: csr table 11.4.1.5.4–2, page 179)

Body Mass Index Category: Reductions in DBP and SBP with FDC treatment in both BMI subgroups (BMI < or ≥ 30 kg/m^2) were numerically greater than reductions observed in patients receiving the corresponding monotherapies

Table 22: Subgroup analysis by BMI category: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	< 30 kg/m^2	*≥ 30 kg/m^2*	*< 30 kg/m^2*	*≥ 30 kg/m^2*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–2.7	–1.7	–4.5	–2.6
FDC 10/160 mg vs Val 160 mg	–3.9	–4.2	–4.0	–3.1
FDC 10/320 mg vs Neb 10 mg	–2.3	–2.4	–3.9	–3.5
FDC 10/320 mg vs Val 320 mg	–3.5	–4.0	–4.1	–2.3
FDC 20/320 mg vs Neb 40 mg	–1.5	–1.1	–3.9	–1.8
FDC 20/320 mg vs Val 320 mg	–3.5	–5.2	–2.9	–3.0

(Applicant table: csr 11.4.1.5.5–2, page 182)

Gender group: In a number of pairwise comparisons, the treatment effect appeared to be somewhat smaller in females than in males.

Table 23: Subgroup analysis by gender: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	Male	*Female*	*Male*	*Female*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–2.3	–1.9	–4.3	–2.4
FDC 10/160 mg vs Val 160 mg	–4.4	–3.5	–4.1	–2.6
FDC 10/320 mg vs Neb 10 mg	–2.2	–2.3	–4.3	–2.9
FDC 10/320 mg vs Val 320 mg	–4.5	–2.8	–4.4	–1.7
FDC 20/320 mg vs Neb 40 mg	–1.1	–1.4	–2.3	–3.1
FDC 20/320 mg vs Val 320 mg	–5.5	–3.1	–4.8	–0.9

(Applicant table: csr table 11.4.1.5.6–2, page 184)

Ethnicity group: In the pairwise comparison for SBP, the point estimate of the treatment effect appeared to be smaller in Hispanics than in non-Hispanics. It was noted that larger reductions in both DBP and SBP were observed for Hispanic patients receiving placebo compared with non-Hispanic patients receiving placebo.

Table 24: Subgroup analysis by ethnicity: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	Hispanic	*Non-Hispanic*	*Hispanic*	*Non-Hispanic*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–2.5	–1.5	–2.6	–3.8
FDC 10/160 mg vs Val 160 mg	–2.9	–4.3	–1.3	–4.7
FDC 10/320 mg vs Neb 10 mg	–1.4	–2.6	–1.9	–4.8
FDC 10/320 mg vs Val 320 mg	–1.9	–4.8	–0.8	–4.7
FDC 20/320 mg vs Neb 40 mg	–0.7	–1.6	–2.0	–3.1
FDC 20/320 mg vs Val 320 mg	–3.5	–5.0	–1.5	–3.9

(Applicant table: csr table 11.4.1.5.7–2, page 187)

Stage 1 and 2 Hypertension at Baseline: In a post hoc analysis, reductions in DBP and SBP were numerically greater in the FDC groups than in the corresponding monotherapies. It seems that was no significant difference between the Stage 1 and Stage 2 groups.

Table 25: Subgroup analysis by stage 1 and stage 2 hypertension: Pairwise comparison of changes from baseline to Week 8 in seated trough diastolic and systolic blood pressure

Pairwise Comparison	*Diastolic Blood Pressure*		*Systolic Blood Pressure*	
	Stage 1 Hypertension	*Stage 2 Hypertension*	*Stage 1 Hypertension*	*Stage 2 Hypertension*
Mean change from baseline after monotherapy subtracted, mm Hg				
FDC 10/160 mg vs Neb 10 mg	–2.4	–2.1	–3.3	–3.8
FDC 10/160 mg vs Val 160 mg	–3.8	–4.3	–3.4	–3.7
FDC 10/320 mg vs Neb 10 mg	–1.4	–2.8	–2.7	–4.3
FDC 10/320 mg vs Val 320 mg	–2.8	–4.2	–3.3	–2.7
FDC 20/320 mg vs Neb 40 mg	–1.9	–1.0	–3.5	–2.5
FDC 20/320 mg vs Val 320 mg	–4.8	–4.2	–3.6	–2.5

(Applicant table: Summary of clinical efficacy table 3.3.2–1, page 58)

Reviewer comments: In subgroup analyses, the FDC at the highest dose of 20/320 mg did not show any benefit for the reduction of either the systolic or diastolic blood pressure in comparison with nebivolol 40 mg in patients who were black or who had diabetes.

FDC 20/320 did not produce a greater reduction in SBP in patients ≥ 65 years old than its corresponding monotherapies. Although the sponsor claimed that this may be related to the

small sample size (368 of 4118 patients) and the significant placebo effect on SBP reduction (-15.1 mmHg), the placebo effect should not affect the final result for the difference between the FDC and each monotherapy after the subtraction of the placebo. The sample size of 368 patients in general should be sufficient for the analysis. The findings raise questions about efficacy in these populations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose-response analysis: Mean reductions in DBP and SBP from baseline at the end of each 4-week treatment phase (Weeks 1-4 and Weeks 5-8) for each FDC treatment group and for the placebo group are summarized in the following tables.

Overall, doubling of each of the FDC doses (FDC 5/80 mg to FDC 10/160 mg, FDC 10/160 mg to FDC 20/320 mg, and FDC 5/160 mg to FDC 10/320 mg) showed an incremental effect on blood pressure reduction, although the size of the effect is small. The incremental effect on blood pressure of doubling the valsartan dose (80 to 160 and 160 to 320) and of increasing the dose of nebivolol from 20 to 40 mg is also small (essentially same as increasing placebo).

Table 26: Reductions in DBP from Week 4 to Week 8—ITT Population

Treatment of Group, Weeks 1-4; Treatment of Group, Weeks 5-8	*DBP at 4 Weeks*	*DBP at 8 Weeks*	*Mean Change, mm Hg*	*p-Value*
Placebo; placebo	93.7	92.9	–0.8	0.0914
Neb 5 mg; Neb 10 mg	89.3	87.2	–2.1	< 0.0001
Neb 20 mg; Neb 40 mg	86.2	85.3	–0.8	0.0146
Val 80 mg; Val 160 mg	89.8	89.0	–0.8	0.0147
Val 160 mg; Val 320 mg	89.0	88.5	–0.6	0.0846
FDC 5/80 mg; FDC 10/160 mg	86.4	84.8	–1.6	< 0.0001
FDC 5/160 mg; FDC 10/320 mg	86.1	84.7	–1.4	< 0.0001
FDC 10/160 mg; FDC 20/320 mg	85.8	84.2	–1.6	< 0.0001

(Applicant table: summary of clinical efficacy, table 3.4.1.1–1, page 64)

Table 27: Reductions in SBP from Week 4 to Week 8—ITT Population

Treatment of Group, Weeks 1-4; Treatment of Group, Weeks 5-8	*SBP at 4 Weeks*	*SBP at 8 Weeks*	*Mean Change, mm Hg*	*p-Value*
Placebo; placebo	148.3	147.2	–1.1	0.1760
Neb 5 mg; Neb10 mg	143.4	140.8	–2.6	< 0.0001
Neb 20 mg; Neb 40 mg	140.7	140.0	–0.7	0.2076
Val 80 mg; Val 160 mg	143.1	141.6	–1.6	0.0031
Val 160 mg; Val 320 mg	140.6	140.3	–0.4	0.4782
FDC 5/80 mg; FDC 10/160 mg	139.5	137.0	–2.5	< 0.0001
FDC 5/160 mg; FDC 10/320 mg	139.5	137.5	–2.0	0.0011
FDC 10/160 mg; FDC 20/320 mg	138.8	136.8	–2.0	0.0004

(Applicant table: summary of clinical efficacy table 3.4.1.2–1, page 65)

Table 28: Difference of DBP and SBP between low dose and high dose at Week 8

	Nebivolol		Valsartan		Nebivolol/Valsartan	
Drug dose	20mg*	40mg	160mg	320mg	10/160mg	20/320mg
DBP	86.2	85.3	89.0	88.5	84.8	84.2
Difference	0.9		0.5		0.6	
SBP	140.7	140	141.6	140.3	137	136.8
Difference	0.7		1.3		0.2	

*dose at the end of week 4 (reviewer's table)

Table 29: Comparison of DBP and SBP among different doses of Nebivolol

	Nebivolol			Difference 10 mg vs 20mg	Difference 20 mg vs 40 mg
Drug dose	10 mg	20 mg*	40 mg		
DBP	87.2	86.2	85.3	1.0	0.9
SBP	140.8	140.7	140	0.1	0.7

*dose at the end of week 4 (reviewer's table)

Reviewer comments: *The sponsor's rationale for proposing the 20 mg dose as the highest dose of nebivolol in the combination study was that the dose response relationship for nebivolol is shallow above 20 mg, with DBP reductions of 1 to 3 mm Hg when doses increase above 20 mg and that the 40mg dose does not provide a significantly better BP response but is associated with an increased incidence of adverse events. Based on the above table, the difference between the 20 mg and 40 mg dose is similar to the difference between the 10 mg and 20 mg dose for DBP, and is better than the difference between the 10 mg and 20 mg for SBP.*

Choice of dose and dosing interval: For the choice of dose, the least squares mean change in DBP and SBP, the percent of DBP responders, the percent of SBP responders, and the percent of patients achieving BP control for each FDC treatment arm at Week 4 (FDC 5/80 mg and FDC 5/160 mg) and at Week 8 (FDC 10/160 mg, FDC 10/320 mg and FDC 20/320 mg) were evaluated.

There does not appear to be a difference in BP reduction or BP control between some of the doses.

Table 30: Efficacy findings for FDC treatment groups

Treatment	DBP reduction (mmHg)	SBP reduction (mmHg)	BP control (%)
FDC 5/80 mg	-13.5	-14.8	45.7
FDC 5/160 mg	-13.8	-15.3	46.5
FDC 10/160 mg	-15.0	-17.0	52.1
FDC 10/320 mg	-15.1	-17.0	52.2
FDC 20/320 mg	-15.7	-17.1	55.3

(Reviewer table)

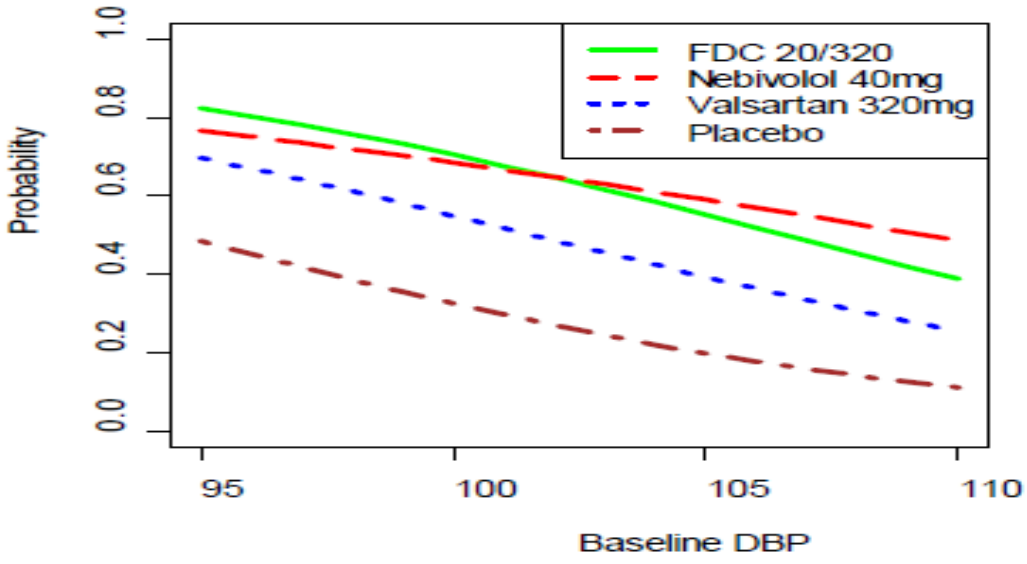
The FDC was dosed once daily, consistent with recommended dosing intervals for the individual components. At all visits, patients in each FDC treatment group had numerically greater BP reductions compared with patients receiving the corresponding monotherapies or placebo; these

differences were observed as early as Week 2 of treatment (the earliest measurement after the baseline). This may imply that dose adjustments could be carried out after about 2 to 4 weeks of dosing as there was no much change after two weeks. If BP remains uncontrolled after 3 weeks of therapy, the dose may be increased to higher dose.

Replacement therapy (substitution for the titrated components): In PK studies, the Cmax and AUC of nebivolol decreased about 43-47% and 16-27%, respectively, in the presence of valsartan. In the presence of nebivolol, valsartan exposure decreased slightly less. Based on the clinical pharmacology review, these PK parameters changes overall would not affect the efficacy of FDC in comparison with each monotherapy.

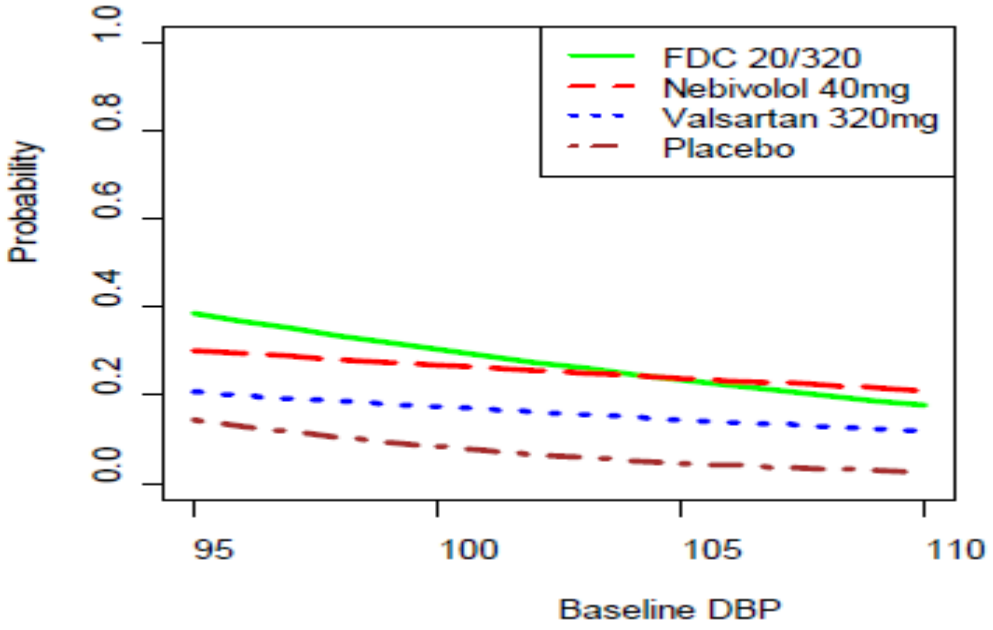
*First-line therapy***:** To address use as first-line therapy, estimates of the probability of reaching a BP goal (systolic BP <140 or 130 mmHg and diastolic BP <90 or 80 mmHg) at endpoint were determined by analyses using a logistic regression model with baseline as a covariant. As shown in the following figures, in all treatment arms the estimated probability of achieving the diastolic goals (80/90 mmHg) decreases as baseline DBP gets higher. For all baseline DBP values, the estimated probability is higher with the FDC 20/320 mg and the nebivolol 40 mg monotherapy than with the valsartan 320 mg monotherapy and placebo. However, there was no difference between FDC 20/320 mg and nebivolol 40 mg. For all baseline SBP values, the estimated probabilities of achieving both goals (130/140 mmHg) with the FDC 20/320 mg appear to be higher than with either the nebivolol 40 mg monotherapy or the valsartan 320 mg monotherapy.

Figure 7: Probability of achieving diastolic blood pressure goal (< 90 mm Hg) with FDC 20/320 mg, nebivolol 40 mg, and valsartan 320 mg



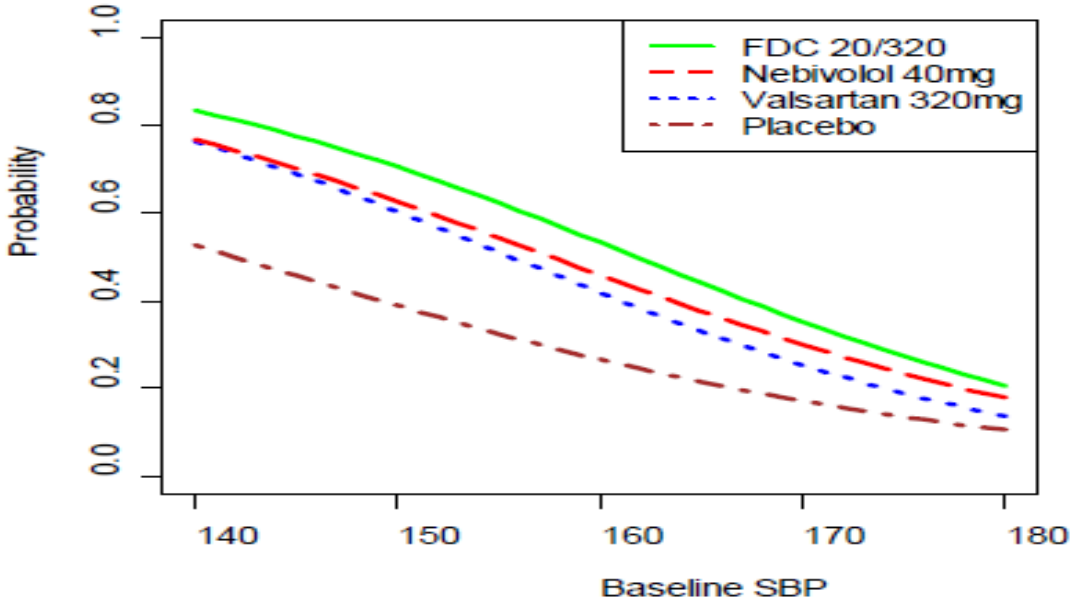
(FDA statistican review figure 4, page 16)

Figure 8: Probability of achieving diastolic blood pressure goal (< 80 mm Hg) with FDC 20/320 mg, nebivolol 40 mg, and valsartan 320 mg



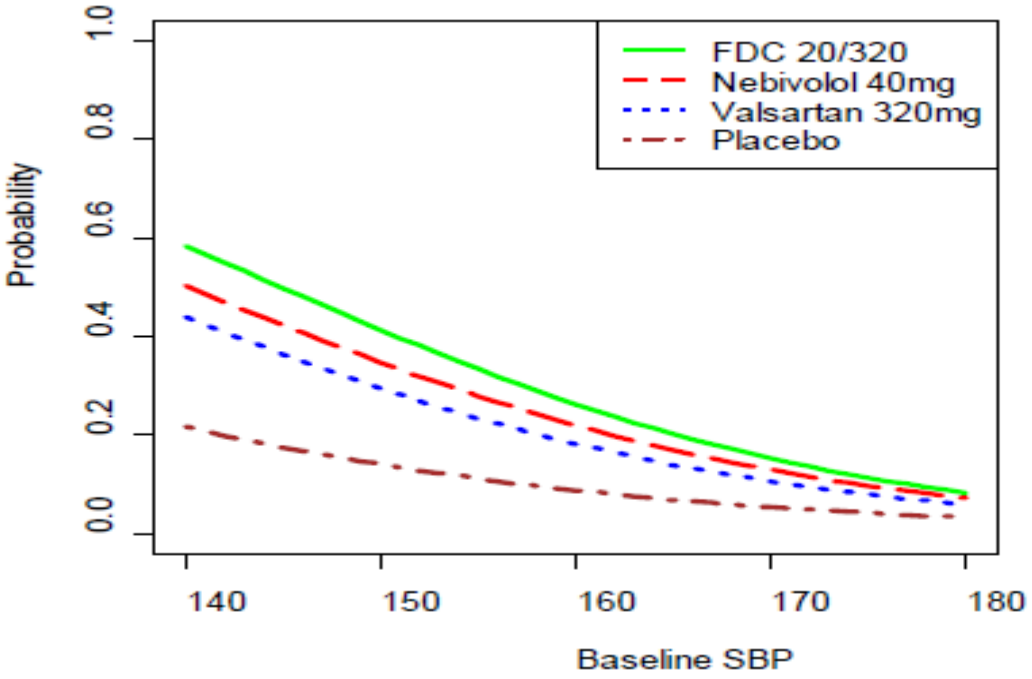
(FDA statistican review figure 5, page 16)

Figure 9: Probability of achieving systolic blood pressure goal (< 140 mm Hg) with FDC 20/320 mg, nebivolol 40 mg, and valsartan 320 mg



(FDA statistican review figure 6, page 17)

Figure 10: Probability of achieving systolic blood pressure goal (< 130 mm Hg) with FDC 20/320 mg, nebivolol 40 mg, and valsartan 320 mg



(FDA statistican review figure 7, page 18)

Reviewer comments: Overall, dose-response for the FDC was shallow for the primary endpoint of DBP and the key secondary endpoint of SBP, as well as blood pressure control rates.

As shown in the figures above, the percentage of subjects achieving DBP goals (< 90 mmHg or <80mmHg) by baseline DBP was similar in the FDC 20/320 mg and Nebivolol 40 mg monotherapy groups. Therefore, the data may not support use as intial therapy in patients who are likely to need multiple drugs to achieve blood pressure goals.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy: Study NAC-MD-02, an open-label, single-arm, 52-week study evaluating the long-term safety/tolerability of nebivolol in free-tablet combination with valsartan in patients with stage 1 or 2 hypertension, provides data on the persistence of blood pressure reduction in comparison with the baseline.

The study showed that long-term maintenance of BP was achieved throughout 52 weeks of treatment with the free-tablet combination of nebivolol and valsartan. Both DBP and SBP reductions observed over up to 52 weeks of treatment in Study NAC-MD-02 were similar in magnitude to those demonstrated in the 8-week pivotal study (15.0 mm Hg to 15.7 mm Hg for DBP and 17.0 mg Hg to 17.1 mm Hg for SBP), and thus represent supportive data. Data are

summarized in the following tables. The reduction in pulse rate observed over 52 weeks also suggests a durable pharmacologic effect (see figure below).

Table 31: Change from baseline in trough seated diastolic blood pressure

Visit	*Free-Tablet Combination (N = 799)*					
	Neb/Val		*Neb/Val/HCTZ*		*All Patients*	
	n	**Change**	**n**	**Change**	**n**	**Change**
Week 2	380	–13.5	418	–10.0	798	–11.7
Week 6	340	–17.2	419	–10.4	759	–13.4
Week 10	308	–18.1	419	–11.7	727	–14.4
Week 14	284	–19.1	419	–12.3	703	–15.0
Week 18	262	–21.0	419	–12.3	681	–15.7
Week 22	236	–21.6	409	–14.4	645	–17.0
Week 28	226	–22.2	404	–17.0	630	–18.8
Week 40	216	–22.3	379	–19.6	595	–20.6
Week 52	206	–19.3	296	–18.7	502	–19.0

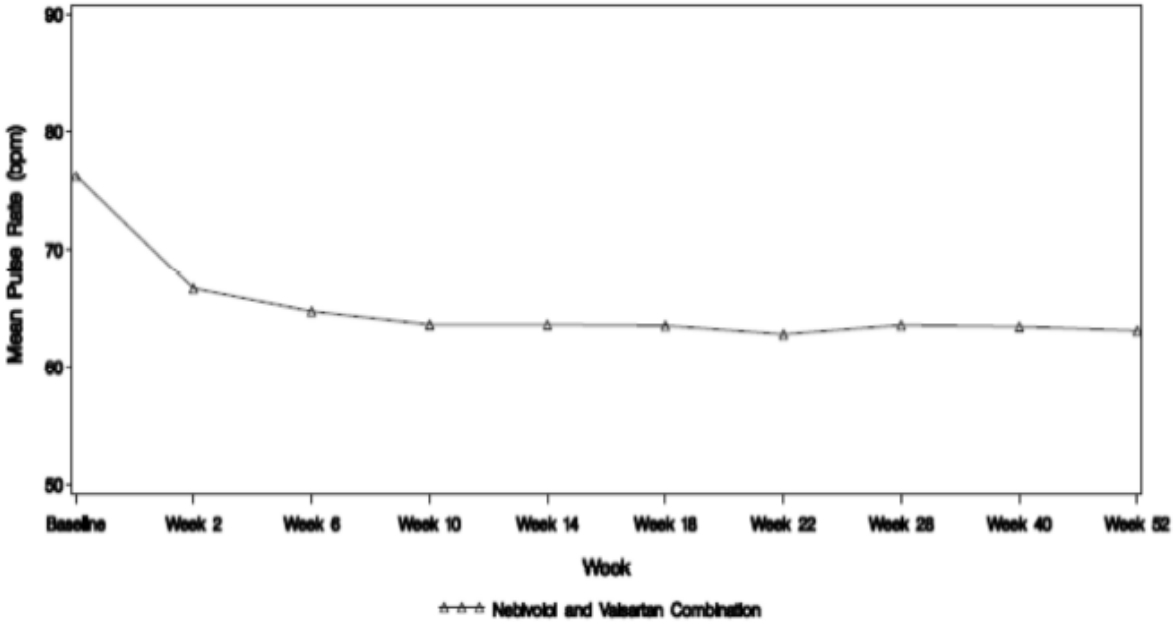
(Applicant table: summary of clinical efficacy table 8.1–12, page 105)

Table 32: Change from baseline in trough seated systolic blood pressure

Visit	*Free-Tablet Combination (N = 799) Mean ± SD*					
	Neb/Val		*Neb/Val/HCTZ*		*All Patients*	
	n	**Change**	**n**	**Change**	**n**	**Change**
Week 2	380	–16.5	418	–10.7	798	–13.5
Week 6	340	–22.1	419	–11.4	759	–16.2
Week 10	308	–23.2	419	–12.3	727	–16.9
Week 14	284	–24.1	419	–13.9	703	–18.0
Week 18	262	–27.0	419	–13.3	681	–18.6
Week 22	236	–29.3	409	–17.9	645	–22.0
Week 28	226	–30.1	404	–22.3	630	–25.1
Week 40	216	–30.4	379	–27.1	595	–28.3
Week 52	206	–26.2	296	–25.0	502	–25.5

(Applicant table: summary of clinical efficacy table 8.1–13, page 106)

Figure 11: Study NAC-MD-02: Change from baseline in pulse rate



(Applicant figure: summary of clinical efficacy figure 3.5.4–1, page 68)

Reviewer's comments: In this long-term study, the percentage of subjects who required the addition of HCTZ was 59% (296 of 502 patients), indicating a control rate with FDC without HCTZ of 41%. This number is lower than the control rate seen with the FDC in the 8-week pivotal study (51.8%) and may provide a more realistic estimate of control rates with the FDC over the long-term. The lack of a control arm makes it somewhat difficult to interpret the data on long–term blood pressure reduction and control.

The effect of treatment withdrawal was not studied with this FDC product. Previous studies have shown that following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred in patients with ischemic heart disease. There is no study report of withdrawal or rebound effects in the prescribing information for valsartan. Therefore, based on the existing data for both monotherapies, when discontinuing chronically administered FDC, particularly in patients with ischemic heart disease, dosage should be reduced gradually over a period of 1-2 weeks as described in the nebivolol labeling.

6.1.10 Additional Efficacy Issues/Analyses
None.

7 Review of Safety

Safety Summary

Safety analyses focused on the data collected in the two phase 3 trials conducted in patients with primary hypertension. Data from six phase 1 studies conducted in healthy volunteers were also utilized in the safety evaluation. Other sources of data included labeling for nebivolol and valsartan monotherapies, postmarketing reports and the published literature on nebiovol and valsartan.

A total of 1664 patients with hypertension were exposed to the nebivolol/valsartan FDC for 8 weeks in the short-term pivotal study, Study NAC-MD-01. A total of 807 patients were exposed to a nebivolol/valsartan free-tablet combination for up to 52 weeks in the long-term, uncontrolled trial, Study NAC-MD-02. The overall mean treatment duration was 59.9 days in the combined FDC treatment group in the short-term pivotal study and 285.7 days with the free-tablet combination in the long-term trial.

- During the double-blind treatment period of the pivotal efficacy trial, the incidence rates of SAEs in the FDC groups were the same as or lower than the incidence rates in the placebo and monotherapy groups. There was no dose-related increase in AEs leading to discontinuation in the FDC treatment groups, and, in general, the incidence of AEs was similar across the nebivolol/valsartan, component monotherapy, and placebo treatment arms.

- A dose-related increase in bradycardia was observed with nebivolol monotherapy (2.0 % of subjects at the 10 mg dose and 6.3% at the 40 mg dose) but not with the FDC product (2.2-2.5% of subjects) in the factorial trial; however, bradycardia AEs leading to patient withdrawal were uncommon. Bradycardia AEs leading to withdrawal were reported in three patients (0.5%) at the 20/320 dose of the FDC as compared to eight subjects (1.4%) at the 40 mg dose of nebivolol in the pivotal efficacy trial.

- Given the safety profiles of nebivolol and valsartan, adverse events of interest also included hypotension/orthostatic hypotension, hyperkalemia and impaired renal function. The overall incidence of these events was low (less than 1%) and there was no significant difference between the combination groups and respective monotherapy groups. The trials, however, excluded patients who might be at greater risk of some of these complications, such as those with significant renal impairment.

- Effects on laboratory parameters (e.g., uric acid, HDL, potassium, triglycerides) and vital signs were also largely consistent with the known effects of the monotherapies. Relative to the placebo group and the valsartan treatment groups, greater reductions in pulse rate from baseline were observed in all FDC and nebivolol treatment groups and correlated with the dose of nebivolol.

- During long-term treatment with the FDC in the long-term trial, no new or significant safety signals were observed. In general, the safety findings were consistent with those observed during FDC treatment in the short-term efficacy study. One SAE of bradycardia was reported and a total of 53 (6.6%) subjects had one or more AEs leading to premature discontinuation of treatment. Bradycardia (1.4%) was the most common AE leading to discontinuation. Increases in serum levels of BUN, creatinine, and uric acid were also observed. These increases were small (≤ 10% from baseline to the end of study) and were not associated with renal AEs and may also be related to the addition of HCTZ in some patients.

In conclusion, the size of the safety database and duration of exposure are adequate to assess the safety of this product. Overall, the safety profile is acceptable for the proposed indication.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed in the section 5.3, safety analyses focused on the two phase 3 clinical studies conducted in patients with primary hypertension (Studies NAC-MD-01 and NAC-MD-02). Data from six phase 1 studies conducted in healthy volunteers were also utilized in the safety evaluation (see table below). Other sources of data that were used in the safety evaluation included labeling for nebivolol and valsartan monotherapies, and also post- marketing reports and the published literature on nebiovol and valsartan.

Table 33: Summary of 6 phase 1 studies in healthy volunteers for safety evaluation

Study Identifier	*Primary Objective of the Study*	*Study Design and Type of Control*	*Test Products; Dose Regimen; Route of Administration*[a]	*Number of Subjects (Randomized or Enrolled/ Safety)*[b]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
Phase 1 Studies							
NAC-PK-01	Pharmacokinetics	Phase 1, single-center, open-label, single-dose, 3-way crossover study	Nebivolol 20-mg tablets, valsartan 320-mg tablets; **Treatment A:** nebivolol 20-mg tablet, single dose (fasted conditions); **Treatment B:** valsartan 320-mg tablet, single dose (fasted conditions); **Treatment C:** nebivolol 20-mg tablet and valsartan 320-mg tablet, single dose (fasted conditions)	24/24	Healthy subjects	3 dosing days separated by a 7-day washout period	Complete; full
NAC-PK-03	Pharmacokinetics and pharmacodynamics	Phase 1, single-center, open-label, 3-way crossover, drug-interaction study	Nebivolol 20-mg tablets, valsartan 320-mg tablets; **Treatment A:** nebivolol 20-mg tablet, once daily (fasted conditions); **Treatment B:** valsartan 320-mg tablet, once daily (fasted conditions); **Treatment C:** nebivolol 20-mg tablet and valsartan 320-mg tablet, once daily (fasted conditions)	30/30	Healthy subjects	7 days in each of 3 treatment periods, separated by a washout of 7 days	Complete; full
NAC-PK-04	Pharmacokinetics (food effect on bioavailability)	Phase 1, single-center, open-label, 2-way crossover, single-dose study	FDC 20/320 mg tablets; **Treatment A:** FDC 20/320 mg tablet, single dose (fasted conditions); **Treatment B:** FDC 20/320 mg tablet, single dose (fed conditions)	32/32	Healthy subjects	2 dosing days separated by a 7-day washout period	Complete; full

NAC-PK-05	Pharmacokinetics	Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose study	Nebivolol 20-mg tablets, valsartan 320-mg tablets, FDC 20/320 mg tablets; **Treatment A:** nebivolol 20-mg tablet and valsartan 320-mg tablet, single dose (fasted conditions); **Treatment B:** FDC 20/320 mg tablet, single dose (fasted conditions)	70/70	Healthy subjects	2 dosing days separated by a 7-day washout period	Complete; full
NAC-PK-06	Pharmacokinetics	Phase 1, multicenter, randomized, open-label, parallel, multiple-dose study	FDC 5/80 mg, 10/160 mg, 20/320 mg; **Treatment A:** FDC 5/80 mg tablet, once daily (fasted conditions); **Treatment B:** FDC 10/160 mg tablet, once daily (fasted conditions); **Treatment C:** FDC 20/320 mg tablet, once daily (fasted conditions)	30/30	Healthy subjects	14 days in each of 3 treatment periods	Complete; full
NAC-PK-07	Pharmacokinetics	Phase 1, single-center, randomized, open-label, 2-way crossover, single-dose study	FDC 10/320 mg tablets (current formulation), FDC 10/320 mg tablets (new formulation); **Treatment A:** FDC 10/320 mg tablet, single dose (current formulation); **Treatment B:** FDC 10/320 mg tablet, single dose (new formulation)	70/70	Healthy subjects	2 dosing days separated by a 7-day washout period	Complete; full

(Applicant table: Tabular Listing page 3-5)

7.1.2 Categorization of Adverse Events

Data were presented according to MedDRA Version 15.1.

An AE was considered to be a TEAE if it was not present before the date of the first dose of investigational product or was present before the date of the first dose of investigational product and increased in severity on or after the date of the first dose of investigational product. An AE that occurred more than 30 days after the date of the last dose of investigational product in a study was not counted as a TEAE.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Given differences in study design, for the most part, data were not pooled across studies. Safety data are presented based on the following groups:

- 8-week pivotal study, Study NAC-MD-01
- 52-week long-term safety and tolerability study, Study NAC-MD-02
- 6 phase 1 studies conducted in healthy volunteers

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 5222 subjects, including 4966 patients with stage 1 or stage 2 essential hypertension and 256 healthy volunteers, were included in the safety analysis of this clinical development program.

Doses and duration of exposure in the two phase 3 trials are summarized in the tables below. There were about 550 subjects in each of the FDC and monotherapy arms in the pivotal study. In the long-term study, about 800 subjects received either FDC or FDC plus HCTZ. The total number of patients and the duration of exposure seem adequate to evaluate the safety of this product.

Table 34: Dose and duration of exposure in Study NAC-MD-01

Exposure	*Placebo (N = 277)*	*FDC 10/160[a] (N = 555)*	*FDC 10/320[b] (N = 555)*	*FDC 20/320[c] (N = 554)*	*NEB 10[d] (N = 555)*	*NEB 40[e] (N = 554)*	*VAL 160[f] (N = 555)*	*VAL 320[g] (N = 554)*	*FDC Combined (N = 1664)*	*NEB Combined (N = 1109)*	*VAL Combined (N = 1109)*
Treatment duration, n (%)											
≥ 1 day	277 (100)	555 (100)	555 (100)	554 (100)	555 (100)	554 (100)	555 (100)	554 (100)	1664 (100)	1109 (100)	1109 (100)
≥ 14 days	272 (98.2)	541 (97.5)	543 (97.8)	546 (98.6)	546 (98.4)	545 (98.4)	540 (97.3)	542 (97.8)	1630 (98.0)	1091 (98.4)	1082 (97.6)
≥ 28 days	258 (93.1)	522 (94.1)	528 (95.1)	532 (96.0)	529 (95.3)	513 (92.6)	523 (94.2)	528 (95.3)	1582 (95.1)	1042 (94.0)	1051 (94.8)
≥ 42 days	249 (89.9)	502 (90.5)	509 (91.7)	519 (93.7)	515 (92.8)	497 (89.7)	511 (92.1)	511 (92.2)	1530 (91.9)	1012 (91.3)	1022 (92.2)
≥ 56 days	244 (88.1)	494 (89.0)	501 (90.3)	509 (91.9)	506 (91.2)	481 (86.8)	501 (90.3)	500 (90.3)	1504 (90.4)	987 (89.0)	1001 (90.3)
Treatment duration, days											
Mean	58.8	59.4	59.9	60.6	60.4	58.9	59.7	60.1	59.9	59.7	59.9
SD	13.2	13.2	12.6	11.1	12.0	13.6	12.9	12.2	12.3	12.9	12.5
Median	63.0	63.0	63.0	63.0	63.0	63.0	63.0	63.0	63.0	63.0	63.0
Min, max	6, 70	1, 73	1, 77	1, 74	1, 84	1, 84	1, 82	1, 96	1, 77	1, 84	1, 96
n	277	555	555	554	555	554	555	554	1664	1109	1109
Patient-years exposure	44.60	90.19	90.97	91.90	91.76	89.40	90.74	91.16	273.06	181.16	181.90

a Patients received FDC 5/80 mg the first 4 weeks and were then up-titrated to FDC 10/160 mg for the next 4 weeks.
b Patients received FDC 5/160 mg the first 4 weeks and were then up-titrated to FDC 10/320 mg for the next 4 weeks.
c Patients received FDC 10/160 mg the first 4 weeks and were then up-titrated to FDC 20/320 mg for the next 4 weeks.
d Patients received nebivolol 5 mg the first 4 weeks and were then up-titrated to nebivolol 10 mg for the next 4 weeks.
e Patients received nebivolol 20 mg the first 4 weeks and were then up-titrated to nebivolol 40 mg for the next 4 weeks.
f Patients received valsartan 80 mg the first 4 weeks and were then up-titrated to valsartan 160 mg for the next 4 weeks.
g Patients received valsartan 160 mg the first 4 weeks and were then up-titrated to valsartan 320 mg for the next 4 weeks.
Patient-years exposure = total amount of time exposed to investigational product defined as (last dose date – first dose date + 1)/365.25, expressed in years.
(Applicant table: summary of clinical safety report- table 1.2.1-1, page 34)

Table 35: Dose and duration of exposure in Study NAC-MD-02

Exposure	*Nebivolol/Valsartan Free-Tablet Combination Only (N = 388)*	*Nebivolol/Valsartan Free-Tablet Combination Plus HCTZ[a] (N = 419)*	*Total (N = 807)*
Treatment duration, n (%)			
≥ 1 day	388 (100)	419 (100)	807 (100)
≥ 14 days	369 (95.1)	419 (100)	788 (97.6)
≥ 28 days	336 (86.6)	419 (100)	755 (93.6)
≥ 42 days	327 (84.3)	419 (100)	746 (92.4)
≥ 56 days	307 (79.1)	419 (100)	726 (90.0)
≥ 180 days	223 (57.5)	398 (95.0)	621 (77.0)
≥ 270 days	212 (54.6)	350 (83.5)	562 (69.6)
≥ 360 days	200 (51.5)	276 (65.9)	476 (59.0)
Treatment duration, days			
Mean	236.4	331.4	285.7
SD	151.8	66.1	124.9
Median	364.0	370.0	368.0
Min, max	1, 389	124, 400	1, 400
Patient-years exposure	251.07	380.20	631.27

a Patients received HCTZ in addition to nebivolol/valsartan free-tablet combination at any time during the study after 10 weeks on 20/320 mg if blood pressure goal not achieved.
Patient-years exposure = total amount of time exposed to investigational product defined as (last dose date – first dose date + 1)/365.25, expressed in years.
(Applicant table: summary of clinical safety report-table 1.2.2-1, page 35)

In both the pivotal study and the long-term open label study, the treatment groups were, for the most part, similar with respect to demographic and baseline characteristic. The trial excluded patients with CKD and that although patients with type 2 diabetes could be enrolled, the trial limited enrollment to those with well-controlled diabetes. Demographic and other baseline characteristics are summarized in the following table.

Table 36: Demographic and physical characteristics in Studies NAC-MD-01 and NAC-MD-02

Parameter	*Study NAC-MD-01 Total Population (N = 4159)*	*Study NAC-MD-02 (N = 807)*
Age, years[a]		
Mean ± SD	51.3 ± 10.2	52.7 ± 9.5
n	4159	807
Age group, years, n (%)[b]		
< 65	3789 (91.1)	733 (90.8)
≥ 65	370 (8.9)	74 (9.2)
Sex, n (%)		
Male	2308 (55.5)	448 (55.5)
Female	1851 (44.5)	359 (44.5)
Race, n (%)		
White	3523 (84.7)	531 (65.8)
All Other Races	636 (15.3)	276 (34.2)
Black/African American	411 (9.9)	245 (30.4)
Asian	149 (3.6)	21 (2.6)
American Indian or Alaska Native	30 (0.7)	3 (0.4)
Native Hawaiian or Other Pacific Islander	13 (0.3)	2 (0.2)
Other	33 (0.8)	5 (0.6)
Ethnicity, n (%)		
Hispanic or Latino	1684 (40.5)	197 (24.4)
Not Hispanic or Latino	2475 (59.5)	610 (75.6)
Weight, kg		
Mean ± SD	92.05 ± 20.75	94.06 ± 20.89
n	4159	807
Height, cm		
Mean ± SD	169.30 ± 10.40	170.00 ± 10.18
n	4158	807
BMI, kg/m^2		
Mean ± SD	32.03 ± 6.19	32.49 ± 6.40
n	4158	807
Type 2 diabetes status, n (%)[c]		
Type 2 diabetes	638 (15.3)	138 (17.1)
Non-diabetes	3521 (84.7)	669 (82.9)

a Age was based on the informed consent date.
b Age categorical for Study NAC-MD-02 was manually calculated
c Patients with type 1 diabetes were excluded from the study.
(Applicant table: summary of clinical safety-table 1.3.1.3-1, page 63)

7.2.2 Explorations for Dose Response

In the pivotal study, drug doses in all treatment groups were doubled at the end of week 4 and then maintained to the end of week 8. See Section 7.5.1 for discussion of dose dependency for adverse events and Section 7.3.3 for discussion of drop outs and discontinuations by dose.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was done.

7.2.4 Routine Clinical Testing

Clinical testing, which included adverse event data collection, laboratory parameter assessments, vital signs and physical examinations, was adequate.

A thorough QT study was not conducted. Both nebivolol and valsartan are approved products. Valsartan is not known to cause QT prolongation. A thorough QT study for nebivolol showed no relationship between the nebivolol plasma concentrations and QTcF.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Section 4.4, Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Based on the safety profiles of beta-blocker antagonists and ATII receptor blockers, the evaluation for potential adverse events was adequate.

7.3 Major Safety Results

7.3.1 Deaths

Five deaths were reported in the two Phase 3 trials. Two patients had SAEs that resulted in death during the single-blind placebo run-in period of Study NAC-MD-01; these were due to a road traffic accident and a cerebrovascular accident. No patient died in the double-blind treatement period in NAC-MD-01. Three patients had SAEs that resulted in death during Study NAC-MD-02; one of these death occurred 8 days after the patient completed the open-label down-titration phase. Causes of death were reported to be gunshot wound, coronary artery occlusion, and cardiac arrest. None of these deaths was considered to be drug-related events.

7.3.2 Non-fatal Serious Adverse Events

In Study NAC-MD-01, a total of 80 SAEs were reported in 64 patients, including 41 SAEs in 33 patients during the single-blind placebo run-in period, 27 SAEs in 23 patients during the double-blind treatment period and 12 SAEs in 8 patients during the double-blind down-titration period. During the double-blind treatment period, the incidence rates of SAEs in the FDC groups were the same as or lower than the incidence rates in the placebo and monotherapy groups as shown in the following table. Similar findings were observed in the double-blind down-titration period.

Based on review of the narratives, none of the SAEs in the FDC groups appeared to be drug-related. See the appendix for the narratives of the SAEs in the FDC groups.

Table 37: Incidence of serious adverse events in study NAC-MD-01

Preferred Term	*Placebo (N = 277, M = 244) n (%) [Related]*	*FDC 10/160 (N = 555, M = 505) n (%) [Related]*	*FDC 10/320 (N = 555, M = 495) n (%) [Related]*	*FDC 20/320 (N = 554, M = 520) n (%) [Related]*	*NEB 10 (N = 555, M = 515) n (%) [Related]*	*NEB 40 (N = 554, M = 501) n (%) [Related]*	*VAL 160 (N = 555, M = 508) n (%) [Related]*	*VAL 320 (N = 554, M = 507) n (%) [Related]*
Double-blind Treatment Period								
Patients with at least 1 on-therapy SAE	**3 (1.1) [0]**	**2 (0.4) [0]**	**2 (0.4) [0]**	**1 (0.2) [0]**	**2 (0.4) [0]**	**4 (0.7) [0]**	**4 (0.7) [0]**	**5 (0.9) [0]**
Diverticulitis	0	0	0	1 (0.2) [0]	0	0	0	0
Acute myocardial infarction	0	0	1 (0.2) [0]	0	0	0	0	1 (0.2) [0]
Appendicitis	0	0	1 (0.2) [0]	0	0	0	0	1 (0.2) [0]
Cerebrovascular accident	1 (0.4) [0]	1 (0.2) [0]	0	0	0	0	0	0
Ankle fracture	0	1 (0.2) [0]	0	0	0	0	0	0
Abortion spontaneous	1 (0.4) [0]	0	0	0	0	0	0	0
Transient ischaemic attack	1 (0.4) [0]	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	1 (0.2) [0]	0	0
Pancreatitis	0	0	0	0	0	1 (0.2) [0]	0	0
Small intestinal obstruction	0	0	0	0	0	1 (0.2) [0]	0	0
Thyroid cancer	0	0	0	0	0	1 (0.2) [0]	0	0
Pyelonephritis acute	0	0	0	0	1 (0.2) [0]	0	0	0
Syncope	0	0	0	0	1 (0.2) [0]	0	0	0
Atrial fibrillation	0	0	0	0	0	0	0	1 (0.2) [0]
Facial bones fracture	0	0	0	0	0	0	0	1 (0.2) [0]
Gastrointestinal haemorrhage	0	0	0	0	0	0	0	1 (0.2) [0]
Pneumonia	0	0	0	0	0	0	0	1 (0.2) [0]
Acute respiratory failure	0	0	0	0	0	0	1 (0.2) [0]	0
Carbon dioxide increased	0	0	0	0	0	0	1 (0.2) [0]	0
Cerebral infarction	0	0	0	0	0	0	1 (0.2) [0]	0
Intracranial aneurysm	0	0	0	0	0	0	1 (0.2) [0]	0
Mental status changes	0	0	0	0	0	0	1 (0.2) [0]	0
Substance abuse	0	0	0	0	0	0	1 (0.2) [0]	0
Suicide attempt	0	0	0	0	0	0	1 (0.2) [0]	0
Double-blind Down-Titration Period								
Patients with at least 1 on-therapy SAE	**1 (0.4) [0]**	**2 (0.4) [0]**	**1 (0.2) [0]**	**0**	**2 (0.4) [0]**	**0**	**2 (0.4) [0]**	**0**
Atrial fibrillation	0	0	1 (0.2) [0]	0	0	0	1 (0.2) [0]	0
Supraventricular tachycardia	0	0	1 (0.2) [0]	0	0	0	0	0
Arthralgia	0	1 (0.2) [0]	0	0	0	0	0	0
Calculus ureteric	0	1 (0.2) [0]	0	0	0	0	0	0
Respiratory failure	0	1 (0.2) [0]	0	0	0	0	0	0
Septic shock	0	1 (0.2) [0]	0	0	0	0	0	0
Cardiac failure congestive	1 (0.4) [0]	0	0	0	0	0	0	0
Non-cardiac chest pain	0	0	0	0	2 (0.4) [0]	0	0	0
Flank pain	0	0	0	0	0	0	1 (0.2) [0]	0
Leukocytosis	0	0	0	0	0	0	1 (0.2) [0]	0

(Applicant table: summary of clinical safety table 2.1.3.1-1, page 103)

The incidence of on-therapy SAEs during the open-label treatment phase and the open-label down-titration phase in Study NAC-MD-02 is summarized in the following table. A total of 39 SAEs were reported in 29 patients during the study including 14 SAEs in 10 patients prior to the open-label treatment phase, 22 SAEs in 17 patients during the open-label treatment phase, and three SAEs in two patients during the open-label down-titration phase.

Table 38: Incidence of serious adverse events during open-label treatment phase and open-label down-titration phase in Study NAC-MD-02

Preferred Term[a]	*Nebivolol/Valsartan Free-Tablet Combination (N = 807, M = 609) n (%) [Related]*
Open-label Treatment Phase	
Patients with at least 1 on-therapy SAE	17 (2.1) [1]
Non-cardiac chest pain	3 (0.4) [0]
Acute myocardial infarction	2 (0.2) [0]
Ankle fracture	1 (0.1) [0]
Anxiety	1 (0.1) [0]
Bradycardia	1 (0.1) [1]
Bronchitis	1 (0.1) [0]
Cardiac arrest	1 (0.1) [0]
Cellulitis	1 (0.1) [0]
Cerebrovascular accident	1 (0.1) [0]
Chronic obstructive pulmonary disease	1 (0.1) [0]
Gun shot wound	1 (0.1) [0]
Hydronephrosis	1 (0.1) [0]
Impetigo	1 (0.1) [0]
Inguinal hernia	1 (0.1) [0]
Ischaemic stroke	1 (0.1) [0]
Lower gastrointestinal haemorrhage	1 (0.1) [0]
Myocardial infarction	1 (0.1) [0]
Renal failure acute	1 (0.1) [0]
Road traffic accident	1 (0.1) [0]
Open-label Down-titration Phase	
Patients with at least 1 on-therapy SAE	2 (0.3) [0]
Coronary artery disease	1 (0.2) [0]
Coronary artery occlusion	1 (0.2) [0]
Electrocardiogram abnormal[b]	1 (0.2) [0]

(Applicant table: summary of clinical safety table 2.1.3.2-1, page 106)

Based on review of the narratives, one SAE of bradycardia may have been drug-related. The narrative of this case is summarized below.

- A 56-year-old female with a 9-year history of hypertension, hypothyroidism since 1995, hyperlipidemia since 2010, obesity (BMI 45.7 kg/m^2) and a more than 20 year smoking history was enrolled in Study NAC-MD-02 and took single-blind placebo for 28 days before receiving open-label nebivolol and valsartan combination for 87 days. The patient received nebivolol 5 mg/valsartan 160 mg for 14 days from (b) (6) to (b) (6) nebivolol 10 mg/valsartan 320 mg for 28 days from (b) (6) to (b) (6) and nebivolol 20 mg/valsartan 320 mg for 45 days from (b) (6) to (b) (6) The patient did not undergo down-titration.

  The patient experienced non-cardiac chest pain and headache on 27 Feb 2012. She presented to the clinic on (b) (6) with chest pain and was found to have elevated blood pressure and bradycardia (blood pressure and heart rate were not provided). She was sent to the emergency department and reported a history of intermittent chest pain for 2 to 3 weeks with significant

worsening on 27 Feb 2012, as well as headache and blurry vision occurring with the chest pain. The chest pain was relieved by rest and deep breathing. She also complained of dyspnea and stated that she had been out of her hypothyroidism medications for 1 month. Upon examination, she complained of fatigue, lightheadedness, blurred vision with tearing, dyspnea associated with chest pain, and right-sided stiffness. She was bradycardic with normal S1 and S2 with no murmurs, rubs, or gallops. According to the narrative, blood pressure was 182/111 mm Hg and 173/95 mm Hg and pulse rate was 42-60 bpm and 81 bpm. An ECG showed sinus bradycardia with a ventricular rate of 40, normal axis, no acute ST elevations or T-wave inversions, PR interval 150, QRS duration 86, QT/QTc 520/434. She was treated with 2 L of oxygen, lisinopril and hydrochlorothiazide, clopidogrel, enoxaparin injection, acetylsalicylic acid, morphine, nitroglycerine as needed, levothyroxine, esomeprazole, ondansetron, promethazine, and docusate. She was admitted to the hospital with diagnoses of symptomatic bradycardia, chest pain, hypothyroidism, obesity, and hyperlipidemia. ECG showed marked sinus bradycardia with a ventricular rate of 49, nonspecific T-wave abnormality, PR interval 148, QRS duration 78, QT/QTc 480/415. An exercise stress test was normal. The patient improved, and blood pressures were 100-130/60-80 mm Hg. On (b) (6) her symptoms of intermittent and noncardiac chest pain and headache and the event of bradycardia were considered resolved, and she was discharged from the hospital. The patient was treated with acetylsalicylic acid 81 mg/day, clopidogrel 300 mg/day and 75 mg/day, docusate sodium 100 mg BID, enoxaparin 100 mg/day, esomeprazole 40 mg BID, topical glyceryl trinitrate 1 unit, levothyroxine 150 μg/day, lovastatin 20 mg/day, IV morphine 1 mg as needed, IV ondansetron 4 mg as needed, and Zestoretic (lisinopril/hydrochlorothiazide) 20/25 mg per day. According to the narrative, the patient was discontinued from the study because of the SAE of bradycardia and the nonserious AE of non-cardiac chest pain; both events resolved on (b) (6) (Study Day 88).

7.3.3 Dropouts and/or Discontinuations

Adverse events leading study discontinuation in Study NAC-MD-01 are described in the tables below. There was no dose-related increase in AEs leading to discontinuation in the FDC treatment groups. Nebivolol 40 mg had the highest AE-related discontinuation rate.

During the double-blind treatment period, bradycardia was the most frequent AE leading to discontinuation. AEs of bradycardia leading to discontinuation occurred most frequently in the nebivolol 40 mg treatment group (8 patients, 1.4%). Two patients each in the FDC 10/160 (0.4%) and 10/320 mg (0.4%) treatment groups and 3 patients each in the FDC 20/320 mg (0.5%) and nebivolol 10 mg (0.5%) treatment groups experienced AEs of bradycardia leading to discontinuation from the study.

Table 39: Adverse events leading study discontinuation in Study NAC-MD-01

	Placebo (277)	NEB 10mg (555)	NEB 40mg (554)	Val 160mg (555)	Val 320mg (554)	FDC 10/160 (555)	FDC 10/320 (555)	FDC 20/320 (554)
Subjects with AEs leading to discontinuation* (%)	10 (3.6)	12 (2.2)	22 (4.0)	10 (1.8)	10 (1.8)	15 (2.7)	9 (1.6)	9 (1.6)
Abdominal pain				1				
Abnormal weight gain			1					
Acute myocardial infarction					1		1	
Acute respiratory failure				1				
Agitation	1							
Alcohol abuse		1						
ALT/AST increase	2	3	2		1		2	1
Angina Pectoris						1		
Apathy					1			
Attention deficit/ hyperactivity disorder	1							
Blood glucose increase						1		
Bradycardia		**3**	**8**			**2**	**2**	**3**
Bronchospasm			2					
Cerebrovascular Accident	1			1		1		
Carbon dioxide increased				1				
Chest discomfort								1
Chest pain (non-cardial)						2		
Congest heart failure								1
Diarrhea							1	
Disorientation	1							
Dizziness	1			1	1	1		
Dyspnea			1		2			1
ECG QT prolonged			1					1
Erythema				1				
Fatigue		**1**	**1**		**3**		**1**	**1**
Gastrointestinal hemorrhage					1			
Glomerular filtration rate decrease							1	
Headache	1	1	3	4	2		1	
Heart sounds abnormal	1							
Hypotension			1			1		
Hyperkalemia		1	1					
Hypertension	3	1	2	1	1			1
Hypertriglyceridemia			1					
Insomnia	1			1	1			
Mental status changes					1			
Migranine						1		
Palpitations								
	Placebo	NEB	NEB	Val	Val	FDC	FDC	FDC

	(277)	10mg (555)	40mg (554)	160mg (555)	320mg (554)	10/160 (555)	10/320 (555)	20/320 (554)
Pneumonia					1			
Presyncope				1				
Pruritus		1						
Pyelonephritis acute		1						
Rash			1		1			
Renal failure acute				1				
Small intestinal obstruction			1					
Somnolence					1			
Substance abuse				1				
Suicide attempt				1				
Tachycardia					1			
Thrombocytopenia				1				
Upper respiratory tract infection	1							
Urticaria		1						
Ventricular extrasystoles						1		
Vertigo						1		

*Subjects with at least one event. (Reviewer table)

Table 40: Comparison of discontinuation among placebo, monotherapy and combination therapy at highest dose level

Reasons for patient discontinuation	Placebo (N=277) n (%)	FDC 20/320 (N=554) n (%)	Nebivolol 40 (N= 555) n (%)	Valsartan 320 (N= 555) n (%)
Any discontinuation	33 (11.9)	48 (8.7)	76 (13.7)	58 (10.5)
Adverse events	10 (3.6)	9 (1.6)	22 (4.0)	9 (1.8)
Bradycardia	0	3 (0.5)	8 (1.4)	0
Withdrawal of consent	5 (1.8)	12(2.2)	18 (3.2)	17 (3.1)

(Reviewer table)

In Study NAC-MD-02, 53 (6.6%) subjects had one or more AEs leading to premature discontinuation of treatment. Bradycardia (1.4%) was the most common AE leading to discontinuation in this study. Overall, the findings in this study are similar to the findings in the pivotal study. Data are summarized in the following table.

Table 41: Adverse events associated with premature discontinuation for more than one patient in Study NAC-MD-02

	Nebivolol/valsartan free- tablet combination n=807 (%)
Subjects with AE leading to discontinuation*	53 (6.6)
Bradycardia	11 (1.4)
Fatigue	4 (0.5)
ALT increase	3 (0.4)
Glomerular filtration rate decrease	3 (0.4)
Acute myocardial infarction	2 (0.2)
Hypertension	2 (0.2)
Dizziness	2 (0.2)
Headache	2 (0.2)
Hypotension	2 (0.2)
Non-cardiac chest pain	2 (0.2)

*Subjects were counted only once within each preferred term (Reviewer table)

7.3.4 Significant Adverse Events

Beyond bradycardia, no other significant adverse events were observed.

7.3.5 Submission Specific Primary Safety Concerns

Based on the safety profiles of valsartan and nebivolol, bradycardia, hypotension, hyperkalemia, and decreased GFR, as well as changes in other laboratory parameters (e.g., uric acid, HDL and triglycerides) are potential safety concerns for this product. Findings related to these potential safety concerns are discussed in other sections of the review; tables summarizing the incidence of AEs of bradycardia, hypotension, hyperkalemia and reduction in GFR are provided below.

- Hypotension AEs were uncommon and AEs of orthostatic hypotension was not reported in the pivotal study. Eight AEs of hypotension including six of hypotension and two of orthostatic hypotension were reported in the long-term trial. None of these subjects dropped out because of hypotension.

- The incidence of hyperkalemia AEs was similar among the FDC and valsartan groups in the pivotal study. None of these subjects dropped out because of this AE. In the long-term study, the incidence rate of hyperkalemia was similar to the pivotal study. As noted elsewhere subjects at greater risk of hyperkalemia (e.g., those with lower GFRs and poorly controlled diabetes) were excluded.

- The incidence of AEs of glomerular filtration rate decrease was slightly higher in FDC groups than in the monotherapy groups (0.9% in FDC vs 0.6% in nebivolol and 0.3% in valsartan). However, none of the cases was considered to be an SAE. In the long-term study, the incidence of these AEs was 1.3%, similar to the incidence in the FDC 10/320 mg dose group in the short-term pivotal study. Three patients (0.4%) dropped out from the long-term study because of a GFR decrease. As previously noted, subjects with GFRs < 60 mL/min were excluded

Table 42: Summary of potentially drug-related adverse events in Study NAC-MD-01

Adverse events	Placebo (N=277) n (%)	FDC 10/160 (N=555) n (%)	FDC 10/320 (N=555) n (%)	FDC 20/320 (N=554) n (%)	NEB 10 (N=555) n (%)	NEB 40 (N=554) n (%)	VAL 160 (N=555) n (%)	VAL 320 (N=554) n (%)
Bradycardia	3 (1.1)	12 (2.2)	13 (2.3)	14 (2.5)	11 (2.0)	35 (6.3)	5 (0.9)	3 (0.5)
Hypotension	0	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0	0
Hyperkalemia	1 (0.4)	1 (0.2)	3 (0.5)	6 (1.1)	5 (0.9)	4 (0.7)	6 (1.1)	3 (0.5)
Reduction of GFR	1 (0.4)	2 (0.4)	8 (1.4)	5 (0.9)	1 (0.2)	6 (1.1)	3 (0.5)	0

(Reviewer table)

Table 43: Summary of potentially drug-related adverse events in Study NAC-MD-02

Adverse events	Nebivolol/valsartan free tablet combination (N=807) n (%)
Bradycardia	25(3.1)
Hypotension	6(0.7)
Hyperkalemia	6(0.7)
Reduction of GFR	11 (1.3)

(Reviewer table)

In addition to the aforementioned potential safety concerns, there was a slightly higher incidence of adverse events of ECG QT prolonged, blood triglycerides increase, and C-reactive protein increase in the FDC 20/320 mg arm in the short-term pivotal study. As shown below, the incidence of these events was low (~1%) in the long-term study.

Table 44: TEAEs occurring at a higher incidence in the FDC groups than in the monotherapy groups in Study NAC-MD-01

Adverse events	Placebo N=277 n (%)	FDC 10/160 N=555 n (%)	FDC 10/320 N=555 n (%)	FDC 20/320 N=554 n (%)	NEB 10 N=555 n (%)	NEB 40 N=554 n (%)	VAL 160 N=555 n (%)	VAL 320 N=554 n (%)
Blood triglycerides increase	2 (0.7)	2 (0.4)	4 (0.7)	**7 (1.3)**	3 (0.5)	1 (0.2)	4 (0.7)	1 (0.2)
C-reactive protein increase	2 (0.7)	3 (0.5)	3 (0.5)	**8 (1.4)**	1 (0.2)	3 (0.5)	0	3 (0.5)
ECG QT prolonged	1 (0.4)	6 (1.1)	3 (0.5)	**14 (2.5)**	1 (0.2)	9 (1.6)	4 (0.7)	2 (0.4)

(Reviewer table)

Table 45: Incidence of adverse events of blood triglycerides increase, C-reactive protein and ECG QT pronged in Study NAC-MD-02

Adverse events	Nebivolol/valsartan free tablet combination (N=807) n (%)
Blood triglycerides increase	10 (1.0)
C-reactive protein increase	9 (1.0)
ECG QT prolonged	7 (1.0)

(Reviewer table)

Reviewer comments: Based on the MAED (MedDRA-Based Adverse Events Diagnostics) tool evaluation, the incidence and severity of the aforementioned potential drug-related adverse events were, for the most part, similar among the FDC and monotherapy groups. The higher incidence of TEAEs of ECG QT prolonged in the FDC 20/320 mg group was not confirmed in the long-term open label study. Only three subjects (one in the FDC 20/320 mg group and one in the nebivolol 40 mg group in the short-term study, and one in the long-term open-label study) dropped out due to an AE of ECG QT prolonged. According to the applicant, each case record (including HR-corrected QT values) was examined for patients with a TEAE of "Electrocardiogram QT prolonged" and no safety, QTc, or concomitant drug issues were observed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As discussed in section 7.3.5, in the short-term pivotal study, TEAEs that were reported at higher incidence in the FDC groups than in the monotherapy groups included glomerular filtration rate (GFR) decreased, blood triglycerides increased, C-reactive protein increased, and ECG QT prolonged. The incidence of these events was low and the observed differences between the arms was small. These events are not considered to pose a significant safety concern.

A greater percentage of subjects in Study NAC-MD-02 had a TEAE than in Study NAC-MD-01 (59.1% in Study NAC-MD-02 compared with 33.3% to 34.8% across FDC treatment groups in Study NAC-MD-01). This difference may be due to the longer duration of treatment in Study NAC-MD-02. No unanticipated AEs or safety signals were observed in this study in comparison with the short-term pivotal study and the known safety profiles of each monotherapy.

Table 46: Treatment-emergent adverse events occurring in ≥ 2% of patients in Study NAC-MD-02

Preferred Term	*Nebivolol/Valsartan Free-Tablet Combination (N = 807) n (%)*
Patients with at least 1 TEAE	477 (59.1)
Headache	46 (5.7)
Nasopharyngitis	40 (5.0)
Upper respiratory tract infection	37 (4.6)
Dizziness	35 (4.3)
Bronchitis	24 (3.0)
Cough	22 (2.7)
Fatigue	21 (2.6)
Back pain	20 (2.5)
Urinary tract infection	20 (2.5)
Bradycardia	19 (2.4)
Sinusitis	19 (2.4)
Oedema peripheral	18 (2.2)

(Applicant table: Summary of clinical safety table 2.1.1-2, page 81)

7.4.2 Laboratory Findings

Hematology: Mean changes in hematology parameters from baseline to the end of treatment were generally small in Study NAC-MD-01 and Study NAC-MD-02. In Study NAC-MD-01, the mean changes in the FDC treatment groups were similar in magnitude to those observed in both the monotherapy and the placebo groups.

In the long-term open label study, no significant clinically meaningful post-baseline shifts in hematology parameters were observed.

Clinical chemistry: Mean changes in chemistry parameters from baseline to the end of the double-blind treatment period were generally small. Mean changes observed in most chemistry assessments for the FDC treatment groups were similar to those observed in the monotherapy and/or placebo groups. Small increases from baseline in mean uric acid levels were observed in the FDC treatment groups. These mean changes were similar to those observed in the nebivolol monotherapy groups and were numerically higher than those observed in the valsartan monotherapy groups. Small increases from baseline in uric acid have been previously reported in clinical studies of nebivolol. In the long-term, open label study, increases were observed in serum levels of BUN, creatinine, and uric acid. These increases were small (≤ 10% from baseline to the end of study) and were not associated with renal AEs; the addition of HCTZ may have played a role in some patients.

The percentages of patients in the FDC treatment groups who had a shift in any chemistry parameter (≥ 5%) were comparable to the percentages in the placebo and/or monotherapy treatment groups as summarized in the following table. There were no observable dose-related shifts in chemistry values in the FDC treatment groups.

Table 47: Shifts at end of double-blind treatment period from normal to high or normal to low values in chemistry parameters in ≥ 5% of patients in Study NAC-MD-01

Laboratory Parameter, Unit	*Direction From Normal*	*Placebo (N = 277) n/N1 (%)*	*FDC 10/160 (N = 555) n/N1 (%)*	*FDC 10/320 (N = 555) n/N1 (%)*	*FDC 20/320 (N = 554) n/N1 (%)*	*NEB 10 (N = 555) n/N1 (%)*	*NEB 40 (N = 554) n/N1 (%)*	*VAL 160 (N = 555) n/N1 (%)*	*VAL 320 (N = 554) n/N1 (%)*
Alanine aminotransferase, U/L	High	22/217 (10.1)	33/428 (7.7)	40/434 (9.2)	33/418 (7.9)	47/447 (10.5)	37/422 (8.8)	48/447 (10.7)	39/437 (8.9)
Aspartate aminotransferase, U/L	High	12/241 (5.0)	26/477 (5.5)	24/470 (5.1)	26/463 (5.6)	30/469 (6.4)	28/459 (6.1)	27/467 (5.8)	20/466 (4.3)
Bilirubin (total), µmol/L	Low	10/246 (4.1)	37/492 (7.5)	34/499 (6.8)	29/514 (5.6)	22/497 (4.4)	26/489 (5.3)	21/493 (4.3)	19/473 (4.0)
C-reactive protein (high sensitivity), mg/L	Low	13/87 (14.9)	28/169 (16.6)	26/172 (15.1)	38/178 (21.3)	30/162 (18.5)	22/156 (14.1)	28/174 (16.1)	30/175 (17.1)
	High	25/87 (28.7)	37/169 (21.9)	41/172 (23.8)	43/178 (24.2)	38/162 (23.5)	46/156 (29.5)	45/174 (25.9)	43/175 (24.6)
Cholesterol (HDL), mmol/L	Low	13/150 (8.7)	60/310 (19.4)	65/303 (21.5)	60/312 (19.2)	46/324 (14.2)	54/302 (17.9)	50/305 (16.4)	38/307 (12.4)
	High	10/150 (6.7)	11/310 (3.5)	7/303 (2.3)	11/312 (3.5)	15/324 (4.6)	17/302 (5.6)	14/305 (4.6)	19/307 (6.2)
Cholesterol (LDL), mmol/L	Low	5/48 (10.4)	19/105 (18.1)	10/101 (9.9)	15/97 (15.5)	22/96 (22.9)	15/96 (15.6)	10/84 (11.9)	24/104 (23.1)
	High	22/48 (45.8)	42/105 (40.0)	32/101 (31.7)	43/97 (44.3)	33/96 (34.4)	34/96 (35.4)	35/84 (41.7)	40/104 (38.5)
Cholesterol (total), mmol/L	High	24/151 (15.9)	49/322 (15.2)	44/317 (13.9)	39/313 (12.5)	58/339 (17.1)	52/315 (16.5)	54/312 (17.3)	45/327 (13.8)
Glucose (fasting), mmol/L	High	42/172 (24.4)	71/334 (21.3)	71/314 (22.6)	65/311 (20.9)	67/339 (19.8)	68/305 (22.3)	75/346 (21.7)	62/319 (19.4)
Potassium, mmol/L	High	4/259 (1.5)	21/521 (4.0)	29/511 (5.7)	24/519 (4.6)	23/532 (4.3)	20/520 (3.8)	17/521 (3.3)	16/514 (3.1)
Triglycerides (fasting), mmol/L	High	25/161 (15.5)	72/294 (24.5)	83/326 (25.5)	66/304 (21.7)	80/328 (24.4)	77/308 (25.0)	59/301 (19.6)	74/319 (23.2)
Uric acid (urate), µmol/L	High	12/219 (5.5)	48/449 (10.7)	60/439 (13.7)	45/444 (10.1)	43/441 (9.8)	40/438 (9.1)	35/452 (7.7)	27/442 (6.1)

N = number of patients in the Safety Population; n = number of patients with nonmissing baseline value and a specific time point in the specific category; N1 = number of patients with nonmissing baseline value and a specific time point in the specific baseline category; Neb = nebivolol; Val = valsartan.
(Applicant table: NAC-MD-01 CSR Table 12.4.2.2.2-1, page 250).

Incidences of post-baseline shifts in chemistry parameters occurring in at least 5% of patients during the 52-week, open-label treatment period in Study NAC-MD-02 are summarized in the following table. In general, the changes were consistent with the pivotal study and the experience with the monotherpies. No new findings were identified other than those discussed in in Section 7.3.5. The lack of a control arms limits interpretation.

Table 48: Postbaseline chemistry changes from normal to high or low value in ≥ 5% of patients in Study NAC-MD-02

Baseline	*End of Study*	*Nebivolol/Valsartan Free-Tablet Combination (N = 807) n/N1 (%)*
Alanine aminotransferase, U/L		
Normal	Low	0/638
Normal	High	55/638 (8.6)
Aspartate aminotransferase, U/L		
Normal	Low	17/693 (2.5)
Normal	High	45/693 (6.5)
Blood urea nitrogen, mmol/L		
Normal	Low	17/747 (2.3)
Normal	High	41/747 (5.5)
C-reactive protein, high sensitivity, mg/L		
Normal	Low	44/247 (17.8)
Normal	High	80/247 (32.4)
Cholesterol, HDL, mmol/L		
Normal	Low	71/444 (16.0)
Normal	High	15/444 (3.4)
Cholesterol, LDL, mmol/L		
Normal	Low	26/104 (25.0)
Normal	High	31/104 (29.8)
Cholesterol, total, mmol/L		
Normal	Low	0/475
Normal	High	91/475 (19.2)
Creatinine, µmol/L		
Normal	Low	2/754 (0.3)
Normal	High	52/754 (6.9)
GFR estimated calculation, mL/min/SSA		
Normal	Low	68/758 (9.0)
Normal	High	0/758
Glucose, fasting, mmol/L		
Normal	Low	1/449 (0.2)
Normal	High	110/449 (24.5)
Potassium, mmol/L		
Normal	Low	3/746 (0.4)
Normal	High	39/746 (5.2)
Triglycerides, fasting, mmol/L		
Normal	Low	0/491
Normal	High	129/491 (26.3)
Uric Acid (urate), µmol/L		
Normal	Low	5/643 (0.8)
Normal	High	141/643 (21.9)

N = number of patients in the Safety Population; n = number of patients with nonmissing baseline value and a specific time point in the specific category; N1 = number of patients with nonmissing baseline value and a specific time point in the specific baseline category.
(Applicant table: summary of clinical safety table 3.2.2.2-1, page 148)

Urinalysis: Mean changes in urinalysis parameters from baseline to the end of the treatment were generally small. There were no clinically meaningful changes in any of the urinalysis parameters that were analyzed.

Reviewer comments: There were no clearly, drug-related new abnormal findings in laboratory examinations in the combination groups in comparison with the monotherapy groups.

7.4.3 Vital Signs

Pulse rate: In the short-term pivotal study, greater reductions in pulse rate from baseline were observed in all FDC and nebivolol treatment groups compared to the placebo group and the valsartan treatment groups. The decreases in pulse rate in the treatment groups with nebivolol, either as monotherapy or in combination with valsartan, are consistent with the pulse-rate lowering mechanism of action of nebivolol and were expected based on previous clinical data for nebivolol. There was no unexpected safety signal in pulse rate or unexpected magnitude of pulse-rate change.

The findings in the long-term study were compatible with those seen in the short term trial and the known effects of nebivolol on heart rate. There was no unexpected safety signal in pulse rate or unexpected magnitude of pulse rate change. The greatest change in pulse rate reduction was observed during the first 2 weeks of treatment (–9.5 bpm from baseline to Week 2), with smaller additional reductions (≤ 2.0 bpm) occurring between the remainder of the time points in the study.

Changes from baseline in mean pulse rate are summarized in the following tables.

Table 49: Change from baseline in mean pulse rate in Study NAC-MD-01

Timepoint	*Placebo (N = 277)*		*FDC 10/160 (N = 555)*		*FDC 10/320 (N = 555)*		*FDC 20/320 (N = 554)*		*NEB 10 (N = 555)*		*NEB 40 (N = 554)*		*VAL 160 (N = 555)*		*VAL 320 (N = 554)*	
	n	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*
Pulse rate, bpm																
Baseline at Week 4	264	78.1 ± 10.8	530	77.7 ± 10.9	529	77.1 ± 10.6	532	78.2 ± 10.8	534	77.1 ± 10.5	521	77.4 ± 10.8	529	77.3 ± 10.5	526	76.9 ± 11.3
Change from baseline to Week 4	264	–2.6 ± 9.0	530	–9.7 ± 10.3	529	–9.7 ± 9.7	532	–12.1 ± 10.5	534	–9.3 ± 10.0	521	–13.5 ± 10.6	529	–2.9 ± 9.7	526	–2.1 ± 10.0
Baseline at Week 8	246	78.2 ± 10.7	494	77.9 ± 10.8	501	77.1 ± 10.5	510	78.3 ± 10.8	510	77.1 ± 10.5	490	77.8 ± 10.6	500	77.2 ± 10.6	500	76.7 ± 11.3
Change from baseline to Week 8	246	–2.9 ± 10.0	494	–11.5 ± 10.3	501	–10.9 ± 10.0	510	–14.0 ± 11.1	510	–11.0 ± 10.1	490	–14.6 ± 11.9	500	–3.1 ± 9.9	500	–2.6 ± 9.9
Baseline at end of study	277	78.0 ± 10.7	549	77.8 ± 11.0	548	77.3 ± 10.7	550	78.2 ± 10.8	552	77.0 ± 10.7	547	77.6 ± 10.8	548	77.5 ± 10.7	547	77.1 ± 11.4
Change from baseline to end of study	277	–0.6 ± 10.0.	549	–3.5 ± 10.1	548	–3.4 ± 10.7	550	–6.6 ± 10.8	552	–3.9 ± 10.1	547	–9.3 ± 11.1	548	–2.0 ± 10.4	547	–1.8 ± 10.4

(Applicant table: summary of clinical safety table 4.1.1.1.1-1, page 185)

Table 50: Change from baseline in mean pulse rate in Study NAC-MD-02

Timepoint	*n*	*Pulse Rate (bpm)*	
		Baseline Mean ± SD	*Change From Baseline Mean ± SD*
Week 2	799	76.2 ± 9.9	–9.5 ± 9.5
Week 6	760	76.3 ± 9.9	–11.5 ± 9.4
Week 10	728	76.3 ± 9.9	–12.7 ± 9.5
Week 14	704	76.4 ± 9.8	–12.8 ± 9.8
Week 18	682	76.5 ± 9.7	–12.9 ± 10.0
Week 22	645	76.5 ± 9.6	–13.7 ± 9.3
Week 28	630	76.4 ± 9.6	–12.9 ± 9.7
Week 40	595	76.3 ± 9.5	–12.9 ± 10.1
Week 52	502	76.5 ± 9.6	–13.4 ± 9.8
End of OLTP	800	76.2 ± 9.9	–11.6 ± 10.6
End of OLDP	603	76.5 ± 9.7	–7.0 ± 9.9

OLTP = open-label treatment phase; OLDP = open-label down-titration phase.
(Applicant table: summary of clinical safety table 4.1.1.3.2-1, page 194)

Blood pressure: Effects on blood pressure are discussed in the efficacy section. The incidence of AEs of hypertension, hypotension and orthostatic hypotension in the short-term pivotal trial and the long-term study is summarized in the following tables. Overall, there were no significant findings for blood pressure related adverse events.

Table 51: Adverse events of hypertension, hypostension and orthostatic hypotension in Study NAC-MD-01

Adverse events	Placebo (N=277) n (%)	FDC 10/160 (N=555) n (%)	FDC 10/320 (N=555) n (%)	FDC 20/320 (N=554) n (%)	NEB 10 (N=555) n (%)	NEB 40 (N=554) n (%)	VAL 160 (N=555) n (%)	VAL 320 (N=554) n (%)
Hypertension	2 (0.5)	1 (0.2)	1 (0.2)	0	0	2 (0.4)	1 (0.2)	1 (0.2)
Hypotension	0	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0	0
Orthostatic hypotension	0	0	0	0	0	0	0	0

(Reviewer table)

Table 52: Adverse events of hypertension, hypotension and orthostatic hypotension in Study NAC-MD-02

Adverse events	Nebivolol/valsartan free tablet combination (N=807) n (%)
Hypertension	1 (0.1)
Hypotension	6 (0.7)
Orthostatic hypotension	2 (0.2)

(Reviewer table)

7.4.4 Electrocardiograms (ECGs)

ECG findings were consistent with the known effects of nebivolol on ventricular heart rate, PR interval and the QT interval. See also section 7.3.5 for further discussion of QT findings.

- In the short-term pivotal study, ventricular heart rate decreased in all FDC and nebivolol monotherapy treatment groups (mean change from baseline of –6.8 bpm to –9.8 bpm) but not in the placebo and valsartan monotherapy treatment groups (mean change from baseline of -0.1 bpm to 0.3 bpm). There were small increases in the PR interval in all FDC and nebivolol monotherapy treatment groups. The mean change from baseline in PR interval was 2.6 msec to 3.8 msec in these groups compared with mean changes of -0.3 msec to 0.9 msec in the placebo and valsartan monotherapy groups.

- The QT interval increased in the FDC and nebivolol monotherapy treatment groups, but there were no clinically significant changes in the QTcF interval.

- In the long-term open-label study, changes in ECG parameters, with the exception of heart rate, were small and not considered to be clinically meaningful. The mean change from baseline was -3.5 (SD =9.4) in ventricular rate.

- Potentially clinically significant changes in ECG parameters (defined as a PR interval ≥ 250 msec, a QRS interval ≥150 msec, a QTc interval > 450 msec for females, a QTc interval > 430 msec for males, or a change from baseline in QTc > 60 msec) were also analyzed. Overall, there were no clinically meaningful differences among the placebo, FDC and monotherapy treatment groups in the short-term pivotal study (see table below). In Study NAC-MD-02, a prolonged QTc and a QTc interval increase of > 60 msec were observed in 4 patients. Given the lack of a control arm, these data are hard to interpret.

Table 53: Mean change from baseline in ECG parameters in Study NAC-MD-01

Parameter, Unit	*Placebo (N = 277)*		*FDC 10/160 (N = 555)*		*FDC 10/320 (N = 555)*		*FDC 20/320 (N = 554)*		*NEB 10 (N = 555)*		*NEB 40 (N = 554)*		*VAL 160 (N = 555)*		*VAL 320 (N = 554)*	
	n	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*	*n*	*Mean ± SD*
Ventricular heart rate, bpm																
Baseline	263	70.7 ± 10.4	536	70.4 ± 10.8	524	69.8 ± 10.1	536	70.4 ± 10.2	542	70.1 ± 10.4	531	70.3 ± 9.8	534	69.9 ± 10.1	525	69.6 ± 10.4
Change from baseline to end of DBTP	263	0.3 ± 8.3	536	−7.0 ± 10.0	524	−6.8 ± 8.7	536	−8.9 ± 9.6	542	−7.0 ± 9.2	531	−9.8 ± 9.2	534	0.1 ± 8.7	525	0.0 ± 8.4
PR interval, msec																
Baseline	263	160.2 ± 20.1	536	159.0 ± 22.4	523	161.9 ± 24.8	533	159.0 ± 22.8	541	160.1 ± 24.6	528	160.3 ± 23.2	532	161.1 ± 23.4	519	160.7 ± 23.7
Change from baseline to end of DBTP	263	0.2 ± 19.8	536	3.0 ± 18.1	523	2.6 ± 15.6	533	3.8 ± 18.9	541	3.7 ± 18.0	528	2.8 ± 18.6	532	−0.3 ± 16.7	519	0.9 ± 13.6
QRS interval, msec																
Baseline	263	90.2 ± 11.3	536	89.4 ± 11.3	524	90.7 ± 10.6	535	90.6 ± 10.9	542	89.6 ± 10.3	530	89.8 ± 10.8	533	90.2 ± 10.3	525	91.2 ± 17.4
Change from baseline to end of DBTP	263	0.2 ± 6.3	536	0.4 ± 7.4	524	0.4 ± 8.0	535	0.6 ± 7.1	542	0.6 ± 6.8	530	0.4 ± 6.9	533	0.7 ± 7.0	525	−0.6 ± 15.1
QT interval, msec																
Baseline	263	392.7 ± 26.5	536	392.9 ± 28.2	524	393.6 ± 26.7	535	392.5 ± 27.7	542	393.4 ± 26.8	530	392.2 ± 27.2	533	392.2 ± 28.8	525	392.6 ± 27.0
Change from baseline to end of DBTP	263	0.5 ± 21.2	536	16.0 ± 24.9	524	14.9 ± 23.7	535	20.7 ± 25.8	542	16.9 ± 25.6	530	25.2 ± 24.9	533	−0.4 ± 25.1	525	−0.7 ± 21.8
QTcB, msec																
Baseline	263	423.8 ± 20.5	536	422.8 ± 20.9	524	421.9 ± 21.5	535	422.5 ± 20.2	542	422.5 ± 20.5	530	422.1 ± 21.1	533	420.9 ± 24.2	525	420.2 ± 20.0
Change from baseline to end of DBTP	263	1.3 ± 17.7	536	−5.6 ± 19.4	524	−6.4 ± 18.4	535	−6.9 ± 18.2	542	−4.8± 19.7	530	−6.1 ± 19.3	533	−1.0 ± 20.7	525	−1.0± 17.6
QTcF, msec																
Baseline	263	412.9 ± 18.3	536	412.3 ± 19.0	524	412.0 ± 19.1	535	412.0 ± 18.6	542	412.3 ± 18.2	530	411.6 ± 19.3	533	410.9 ± 22.0	525	410.5 ± 18.0
Change from baseline to end of DBTP	263	1.0 ± 15.6	536	1.8 ± 16.5	524	0.9 ± 16.5	535	2.5 ± 16.0	542	2.6 ± 17.7	530	4.5 ± 16.5	533	−0.8 ± 19.0	525	−0.9 ± 15.6

QTcB = QT interval corrected for heart rate using the Bazett formula (QTcB = QT/(RR)½);
QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓);
DBTP = double-blind treatment period
(Applicant table: summary of clinical safety table 4.2.1.1-1, page 206)

Table 54: Mean change from baseline in ECG parameters in Study NAC-MD-02

ECG Parameter, Unit	*n*	*Baseline Mean ± SD*	*Change From Baseline Mean ± SD*
Summary PR duration, msec	710	165.5 ± 24.9	2.5 ± 18.4
Summary QRS duration, msec	712	90.6 ± 11.7	1.6 ± 9.4
Summary QT interval, msec	712	394.4 ± 26.3	9.1 ± 24.6
QTcB, msec	712	420.6 ± 21.4	−2.0 ± 20.5
QTcF, msec	712	411.5 ± 19.4	1.7 ± 17.5
Summary ventricular rate, beats/min	712	69.0 ± 9.3	−3.5 ± 9.4

QTcB = QT interval corrected for heart rate using the Bazett formula (QTcB = QT/(RR)½);
QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓);
(Applicant table: summary of clinical safety table 4.2.1.2-1, page 207)

Table 55: Incidence of potentially clinically significant post-baseline ECG values in Study NAC-MD-01

ECG Parameter, Unit PCS Criterion	*Placebo (N = 277) n/N1 (%)*	*FDC 10/160 (N = 555) n/N1 (%)*	*FDC 10/320 (N = 555) n/N1 (%)*	*FDC 20/320 (N = 554) n/N1 (%)*	*NEB 10 (N = 555) n/N1 (%)*	*NEB 40 (N = 554) n/N1 (%)*	*VAL 160 (N = 555) n/N1 (%)*	*VAL 320 (N = 554) n/N1 (%)*
Any PCS ECG parameter	**3/263 (1.1)**	**3/535 (0.6)**	**2/524 (0.4)**	**3/535 (0.6)**	**4/541 (0.7)**	**3/530 (0.6)**	**2/533 (0.4)**	**6/525 (1.1)**
PR interval, msec								
≥ 250	1/263 (0.4)	0/534	0/518	0/531	1/539 (0.2)	2/528 (0.4)	1/531 (0.2)	3/517 (0.6)
QRS interval, msec								
≥ 150	0/263	0/534	0/524	0/534	1/541 (0.2)	0/529	0/533	0/524
QTcB, msec								
Male, > 430 and an increase > 60	2/103 (1.9)	0/220	0/221	1/239 (0.4)	1/239 (0.4)	1/229 (0.4)	0/259	2/224 (0.9)
Female, > 450 and an increase > 60	0/105	1/210 (0.5)	0/186	0/192	1/208 (0.5)	0/205	1/181 (0.6)	1/221 (0.5)
QTcF, msec								
Male, > 430 and an increase > 60	1/130 (0.8)	1/279 (0.4)	2/280 (0.7)	3/290 (1.0)	0/282	1/271 (0.4)	0/307	1/274 (0.4)
Female, > 450 and an increase > 60	0/121	2/242 (0.8)	0/223	0/225	1/244 (0.4)	0/239	0/208	0/245

(Applicant table: summary of clinical safety table 4.2.2.1-1, page 209)

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted with this product.

7.4.6 Immunogenicity

Nebivolol and vasartan are both small molecules that by themselves should have little immunogenic potential. Based on availale data, no immunogenicity signal was detected from either the combination or each monotherapy.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As shown in the table below, a dose-related increase in bradycardia was observed with nebivolol monotherapy (2.0 % of subjects at the 10 mg dose and 6.3% at the 40 mg dose) but not with the FDC product (2.2-2.5% of subjects) in the factorial trial. There was also a dose-related increase in fatigue with nebivolol monotherapy (1.8 % of subjects at the 10 mg dose and 4.0% at the 40 mg dose) but not with the FDC product.

Table 56: Summary of dose-dependent adverse events in Study NAC-MD-01

Adverse events	Placebo (N=277) n (%)	FDC 10/160 (N=555) n (%)	FDC 10/320 (N=555) n (%)	FDC 20/320 (N=554) n (%)	NEB 10 (N=555) n (%)	NEB 40 (N=554) n (%)	VAL 160 (N=555) n (%)	VAL 320 (N=554) n (%)
Bradycardia	3 (1.1)	12 (2.2)	13 (2.3)	14 (2.5)	11 (2.0)	35 (6.3)	5 (0.9)	3 (0.5)
Fatigue	6 (2.2)	12 (2.2)	17 (3.1)	13 (2.4)	10 (1.8)	22 (4.0)	14 (2.5)	10 (1.8)

(Reviewer table)

7.5.2 Time Dependency for Adverse Events

The timing of common TEAEs (before Week 4 and between Week 4 and Week 8) was examined in the pivotal trial. In general, there were no marked changes in the occurrence of TEAEs between the two treatment periods other than an increase in the incidence of bradycardia likely reflective the increase in nebivolol dose. The incidence of bradycardia was higher in the 40 mg (after week 4) than in the 20 mg (before week 4) arm (i.e, after the dose was doubled in these subjects).

Table 57: Time related change of bradycardia in Study NAC-MD-01

Before Week 4								
	Placebo (N=277) n (%)	FDC 5/80 (N=555) n (%)	FDC 5/160 (N=555) n (%)	FDC 10/160 (N=554) n (%)	NEB 5 (N=555) n (%)	NEB 20 (N=554) n (%)	VAL 80 (N=555) n (%)	VAL 160 (N=554) n (%)
Bradycardia	2 (0.7)	3 (0.5)	4 (0.7)	3 (0.5)	3 (0.5)	6 (1.1)	1 (0.2)	2 (0.4)
Between Week 4 and Week 8								
	Placebo (N=277) n (%)	FDC 10/160 (N=555) n (%)	FDC 10/320 (N=555) n (%)	FDC 20/320 (N=554) n (%)	NEB 10 (N=555) n (%)	NEB 40 (N=554) n (%)	VAL 160 (N=555) n (%)	VAL 320 (N=554) n (%)
Bradycardia	0	9 (1.7)	9 (1.7)	11(2.1)	8 (1.4)	29 (5.6)	4 (2.8)	2 (0.4)

(Reviewer table)

In the 52-week long-term uncontrolled trial, the incidence of common TEAEs (defined as ≥ 2% incidence) was examined over different periods (≤ 14 weeks, > 14 weeks and ≤ 28 weeks, > 28 and ≤ 40 weeks, and > 40 weeks) in the Safety Population. The highest incidence of common TEAEs (18.4%) occurred in the "≤ 14 weeks" time interval. The highest incidence of common AEs and drug-related AEs including bradycardia, fatigue, etc, was in the first 28 weeks.

Table 58: Common treatment-emergent adverse events (≥ 2% Incidence) by time in Study NAC-MD-02

Preferred Term	*Nebivolol/Valsartan Free-Tablet Combination With and Without HCTZ[a] (N = 807) n (%)*						
	≤ 14 wks	*> 14 and ≤ 28 wks*		*> 28 and ≤ 40 wks*		*> 40 wks*	
	NEB/ VAL N1 = 799 n (%)	NEB/ VAL N1 = 316 n (%)	NEB/ VAL/ HCTZ N1 = 389 n (%)	NEB/ VAL N1 = 221 n (%)	NEB/ VAL/ HCTZ N1 = 391 n (%)	NEB/VAL N1 = 211 n (%)	NEB/ VAL/ HCTZ N1 = 367 n (%)
Patients with at least 1 Common TEAE	**147 (18.4)**	**48 (15.2)**	**31 (8.0)**	**10 (4.5)**	**21 (5.4)**	**14 (6.6)**	**16 (4.4)**
Headache	29 (3.6)	6 (1.9)	4 (1.0)	2 (0.9)	2 (0.5)	3 (1.4)	2 (0.5)
Nasopharyngitis	29 (3.6)	9 (2.8)	3 (0.8)	0	0	1 (0.5)	2 (0.5)
Upper respiratory tract infection	17 (2.1)	6 (1.9)	4 (1.0)	2 (0.9)	7 (1.8)	6 (2.8)	2 (0.5)
Dizziness	17 (2.1)	3 (0.9)	7 (1.8)	4 (1.8)	1 (0.3)	3 (1.4)	4 (1.1)
Bronchitis	13 (1.6)	4 (1.3)	4 (1.0)	0	4 (1.0)	0	0
Cough	11 (1.4)	3 (0.9)	1 (0.3)	0	2 (0.5)	4 (1.9)	2 (0.5)
Fatigue	16 (2.0)	4 (1.3)	2 (0.5)	0	1 (0.3)	0	0
Back pain	7 (0.9)	4 (1.3)	3 (0.8)	3 (1.4)	2 (0.5)	2 (0.9)	1 (0.3)
Urinary tract infection	11 (1.4)	2 (0.6)	2 (0.5)	2 (0.9)	2 (0.5)	0	2 (0.5)
Bradycardia	12 (1.5)	2 (0.2)	3 (0.8)	0	1 (0.3)	1 (0.5)	1 (0.3)
Sinusitis	13 (1.6)	4 (1.3)	0	0	1 (0.3)	1 (0.5)	1 (0.3)
Oedema peripheral	5 (0.6)	9 (2.8)	1 (0.3)	0	1 (0.3)	0	2 (0.5)

(Applicant table: summary of clinical safety table 2.1.1.4.2-1, page 98)

7.5.3 Drug-Demographic Interactions

To evaluate possible effects of demographic factors on the safety of nebivolol and varsatan combination therapy, subgroup analyses were performed by age, gender and race for safety parameters including AEs, laboratory assessments (hematology and clinical chemistry), and vital signs. In general, there was no suggestion of a drug-demographic interaction. The number of subjects age 65 years or older was small. Based on the available, older patients (> 65 years of age) appear to have a higher incidence of bradycardia on the FDC product and nebivolol monotherapy as compared to younger patients.

AEs by age: In patient treated with the FDC or nebivolol monotherapy in the short-term pivotal study, the incidence of bradycardia appeared to be higher in subjects ≥ 65 years of age than in subjects < 65 years of age as shown in the following table. In both age groups, the incidence of bradycardia was greatest with nebivolol 40 mg.

Table 59: Age comparison of bradycardia in Study NAC-MD-01

< 65 Years								
	Placebo (N=250) n (%)	FDC 10/160 (N=511) n (%)	FDC 10/320 (N=510) n (%)	FDC 20/320 (N=513) n (%)	NEB 10 (N=500) n (%)	NEB 40 (N=500) n (%)	VAL 160 (N=505) n (%)	VAL 320 (N=500) n (%)
Bradycardia	2 (0.8)	11(2.2)	11(2.2)	12(2.4)	7(1.4)	30(6.0)	5(1.0)	3(0.3)
≥ 65 to < 75 Years								
	(N=26) n (%)	(N=38) n (%)	(N=44) n (%)	(N=41) n (%)	(N=52) n (%)	(N=45) n (%)	(N=44) n (%)	(N=50) n (%)
Bradycardia	0	1(2.6)	2(4.6)	2(4.8)	3 (5.7)	3 (6.7)	0	0
≥ 75 Years								
	(N=1) n (%)	(N=6) n (%)	(N=1) n (%)	(N=0) n (%)	(N=3) n (%)	(N=9) n (%)	(N=6) n (%)	(N=4) n (%)
Bradycardia	0	0	0	0	1(33.3)	1(11.1)	0	0

(Reviewer table)

In the long-term study, however, the incidence of bradycardia was higher in the group < 65 years of age than in those ≥ 65 (18 /733, 2.5% and 1/65, 1.5%, respectively). This may also be related to the use of HCTZ.

AEs by gender: The incidence of TEAEs was similar in males and females in both the short-term pivotal study and the long-term study. In both studies, headache was generally reported more frequently in females than in males including the placebo group. AEs of fatigue, dizziness, and bradycardia generally occurred at similar rates in males and females across studies and treatment groups.

AEs by race: The incidence of TEAEs was similar across the subgroups (e.g., white, black/African American, and other races) in both the short-term pivotal study and the long-term trial. AEs of headache, fatigue, dizziness, and bradycardia generally occurred at similar rates in all race subgroups across studies and treatment groups.

7.5.4 Drug-Disease Interactions

Common adverse events were analyzed in patients with obesity, diabetes, or renal impairment. In general, there was no clear evidence of differential rates of TEAEs in these three populations in comparison with the overall population. As previously noted, the trials excluded patients with significant renal disease (e.g., GFR < 60 mL/min) and patients with diabetes that was not well-controlled (as defined by a HbA1c value of ≥8%). These data are discussed briefly below:

Obesity: The incidence of TEAEs was similar in non-obese and obese subjects in the pivotal study and long-term trial. While there was a greater incidence of bradycardia in non-obese patients than in obese patients in Study NAC-MD-02, the incidence of bradycardia was similar between these subgroups in Study NAC-MD-01. AEs of fatigue, headache, and dizziness generally occurred at similar rates between the subgroups and across both studies.

Diabetes: The incidence of TEAEs was similar in subjects with and without diabetes in both studies. Bradycardia, fatigue, headache, dizziness, and other common AEs generally occurred at similar rates, as compared between the subgroups and across both studies.

Renal impairment: The incidence of TEAEs was similar between the subgroups of patients with normal renal function and patients with mildly decreased renal function. Due to the low number of patients with moderately decreased renal function, no meaningful conclusions can be drawn regarding the risk of AEs in these patients. In both studies, AEs of headache, dizziness, and bradycardia generally occurred at similar rates. Among patients treated with the FDC product, the incidence of fatigue was slightly greater in patients with mildly decreased renal function than in patients with normal renal function (1.1%, 2.9%, 2.4% vs 0.6%, 1.3% and 1.4%, respectively at doses of 10/160, 10/320 and 20/320 mg).

7.5.5 Drug-Drug Interactions

See discussion in Section 4.4, Clinical Pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No cancer related AE was reported with the combination in the long-term study. Available data for valsartan and nebivolol monotherapy do not suggest human carcinogenicity potential. Therefore, the risk of human carcinogenicity with this FDC product should be low.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate or well-controlled studies of nebivolol/valsartan FDC in pregnant or lactating women and no reproductive toxicology studies have been conducted with the nebivolol/valsartan FDC product to date.

According to the Bystolic label (2011), nebivolol is pregnancy category C as there are no adequate and well-controlled studies of its use in pregnant women; it is not known whether nebivolol is excreted in human milk. According to the Diovan label (2012), valsartan is pregnancy category D and should be discontinued as soon as possible when pregnancy is detected; it is not known whether valsartan is excreted in human milk.

Eleven pregnancies were reported in the short-term pivotal study; however, most of these occurred during the screening period and hence the subjects were not enrolled. Two pregnancies were reported in study participants during the 8-week, double-blind treatment period. One patient was on FDC 10/320 mg and the other was on placebo. The patient on FDC 10/320 mg was a 37-year-old female who started treatment on 02 Nov 2012. The patient's last menstrual period was on 03 Nov 2012. On 14 Dec 2012, the patient had a serum pregnancy test that was positive. Investigational product was discontinued and the patient was withdrawn from the study. The patient delivered a newborn male on (b) (6) by normal vaginal delivery. On (b) (6) trisomy 21 (Down syndrome) was confirmed with high-resolution chromosomal analysis. The mother's family history was significant for Down syndrome in a paternal cousin. The applicant performed an electronic search of relevant information (using sources including, for example, the sponsor-held nebivolol safety database, available valsartan information, and the published

literature) and found no prior reports of the components of the investigational product or drugs in their classes as causative of or associated with Down syndrome or trisomies.

Two pregnancies were reported during the long-term open label study. Both pregnancies occurred during the 52-week, open-label treatment phase. Their narratives are as follows:

- A 35-year-old female with a 4-year history of hypertension and obesity (BMI 46.8 kg/m^2) was initiated on nebivolol/valsartan on 08 Nov 2011. Relevant concomitant medication included Cilest (ethinylestradiol and norgestimate), which was started in April 2011.

  The patient received nebivolol 5 mg/valsartan 160 mg for 14 days from 08 Nov 2011 to 21 Nov 2011, nebivolol 10 mg/valsartan 320 mg for 91 days from 22 Nov 2011 to 20 Feb 2012, and nebivolol 20 mg/valsartan 320 mg for 1 day on 21 Feb 2012. Other than the positive pregnancy test, there were no relevant potentially clinically significant laboratory results, vital signs, ECG results, or additional diagnoses. There were no relevant AEs at the time of the positive pregnancy test. On 05 Apr 2012, the patient developed hypothyroidism and gestational diabetes. On 27 Sep 2012, the patient developed cholestasis of pregnancy. On (b) (6) the patient delivered a healthy male with a gestational age 34.1 weeks (preterm). The newborn's weight was 6 lbs 1 oz, the length was 18.5 inches, and APGAR scores at 1 and 5 minutes were 9. The duration of labor was 1 hour and 25 minutes. There were no complications during the vaginal delivery, and there were no malformation or anomalies at birth. On (b) (6) the gestational diabetes resolved. On 14 Nov 2012, the cholestasis of pregnancy resolved. At the time of reporting, the hypothyroidism was ongoing.

- A 35-year-old female with a 6-year history of hypertension and obesity (BMI 37.1 kg/m^2) was initiated on nebivolol/valsartan on 29 Nov 2011. She was not taking any concomitant medications.

  The patient received nebivolol 5 mg/valsartan 160 mg for 15 days from 29 Nov 2011 to 13 Dec 2011 and nebivolol 10 mg/valsartan 320 mg for 27 days from 14 Dec 2011 to 09 Jan 2012. On 10 Jan 2012 (Study Day 43), the patient had a positive serum pregnancy test at a scheduled site visit. The patient was withdrawn from the study because of the pregnancy. The last dose of investigational product was administered on 09 Jan 2012, after 42 days of treatment. The estimated gestational age at the time of the exposure was 3 weeks, and the estimated date of delivery was 20 Sep 2012. On (b) (6) the patient had a spontaneous abortion. Other than the positive serum pregnancy test, there were no other relevant potentially clinically significant laboratory results, vital signs, ECG results, or additional diagnoses. The patient had no other AEs during the study

There were three pregnancies during the Phase 1 studies. One was discovered before the patient received investigational product. The pregnancy outcome for PID 001-0041 in Study NAC-PK-05 (single-dose) was not provided. PID 001-0006 in Study NAC-PK-06 (2-week multiple dose) delivered a healthy baby girl at 40 weeks gestation.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor did not conduct pediatric studies. Safety and efficacy have not been established in the pediatric population for either monotherapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose: There have been no reports relevant to overdose with the nebivolol/valsartan FDC product in the FDC development program.

Nebivolol overdose has been reported in the post market experience. The most common signs and symptoms associated with Bystolic overdosage are bradycardia and hypotension. Limited data are available related to valsartan overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation.

Drug abuse potential: Nebivolol and valsartan are not structurally or pharmacologically related to any drug known to cause abuse or dependence. During clinical trials with the FDC, there were no AEs that could be indicative of abuse or dependence potential. The risk of abuse or dependence with the combination of nebivolol and valsartan is considered very low.

Withdrawal and Rebound: Withdrawal of some beta-blockers has been associated with an increased risk of myocardial infarction and chest pain, and rapid withdrawal of any antihypertensive drug may lead to a BP increase above pretreatment values or symptoms such as palpitations, chest pain, and tremor.

In a randomized withdrawal study of nebivolol, patients with stage 1 or stage 2 hypertension were treated with nebivolol for 12 weeks; subjects achieving BP control were then randomized to 4 weeks of continued nebivolol treatment (n = 102) or withdrawal to placebo (n = 105). In the withdrawal phase, nebivolol and placebo groups demonstrated mean DBP increases of 1.8 and 7.7 mm Hg, respectively ($p < 0.001$), and SBP increases of 3.5 and 7.6 mm Hg ($p = 0.011$). Twenty-three (22.5%) nebivolol-treated and 18 (17.1%) placebo-treated participants experienced a TEAE. No AEs associated with beta-blocker withdrawal and/or considered causally related to nebivolol were reported. Nebivolol withdrawal resulted in a mean BP increase to near pretreatment levels and was not associated with rebound hypertension.

According to labeling for valsartan, abrupt withdrawal of valsartan has not been associated with a rapid increase in BP.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

A nebivolol/valsartan FDC product has not been marketed in any country. The postmarketing experience with the approved monotherapies is described in the nebivolol and valsartan labels.

9 Appendices

9.1 Literature Review/References

I searched Pubmed with the key words: "adverse events" and "nebivolol," "vasartan," and "nebivolol and vasartan." No additional safety concerns were identified.

9.2 Labeling Recommendations

Labeling recommendations will be discussed separately.

9.3 Advisory Committee Meeting

In the pivotal trial, there was a greater reduction in systolic and diastolic blood pressure in the FDC treatment groups than in the placebo and respective monotherapy treatment groups. However, the difference in mean seated diastolic blood pressure between the highest dose of the FDC and the highest dose of nebivolol was small (~1.2 mmHg). An advisory committee meeting is being held to discuss the clinical significance of this finding.

9.4 Narratives of SAEs in FDC groups

1. SAE of cerebrovascular accident associated with premature study discontinuation at 5/80 mg (10/160 mg group): A 42-year-old male with a 3-year history of hypertension. The patient's other relevant medical history included chronic back pain. The patient was also overweight (BMI 25.7 kg/m^2). Concomitant medications included Vicodin. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 31 days from (b) (6) to (b) (6) and was then randomized to fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/80 mg for 3 days from (b) (6) to (b) (6). The patient did not undergo down-titration.

   On (b) (6) (Study Day 3), the patient was doing laundry at home when he experienced a headache and left eye pain. He noticed he did not have good control of his arms, and he developed slurred speech. He called a friend who reported the patient was having difficulty communicating; he did not make sense, and his words were significantly slow. All of his movements were significantly slowed, and he experienced generalized weakness and dizziness. His roommate drove him to the emergency room and he was admitted. While in the emergency room, he received acetylsalicylic acid. Blood pressure was 173/125, 157/103, and 141/94 mm Hg. Aside from his history of hypertension, the patient did not have other usual risk factors for stroke or atherosclerosis. A urine toxicology screen was positive for opiates. A magnetic resonance imaging scan showed he had had a stroke (there were 2 small foci with diffusion and subtle signal abnormalities near the left caudate head along the left corona radiata and caudate). The neurologic symptoms resolved, but he had a left frontal and retro-orbital headache that was dull and non-throbbing that would come and go. The treatment plan was to try to balance between permissive hypertension and controlling the blood pressure when it was elevated and symptomatic. Clopidogrel was started, and a neurologic consult were requested. On (b) (6) (b) (6) an echocardiogram showed an ejection fraction of 68%, no intracardiac masses or thrombus, no pericardial effusion, sinus rhythm, normal left ventricular wall motion and systolic function, normal left ventricular diastolic function, mild thickening of the left ventricular septum without obstruction, mild mitral regurgitation, mild tricuspid regurgitation, moderate pulmonary hypertension, and negative bubble study. Carotid ultrasound showed no hemodynamically significant stenosis. Total cholesterol was 178 with low-density lipoprotein 93, high-density lipoprotein 26, and triglycerides 293 (units and reference ranges were not provided). He was started on gemfibrozil. The patient's blood pressure came down to the range of 130-149/78-100 mm Hg. A hypercoagulable panel was drawn, and the results

were pending. On (b) (6), the event was resolved without sequelae, and the patient was discharged. He was discontinued from the study because of the cerebrovascular accident, which resolved on (b) (6) (Study Day 5).

2. SAEs of arthralgia, respiratory failure, and septic shock at FDC 10/160mg: A 70-year-old male with a 7-year history of hypertension. The patient's other relevant medical history included knee arthroplasty (right) in 1993; knee arthroplasty (left) in December 1994; hyperlipidemia and spinal column stenosis since 2005; gastroesophageal reflux disease and intervertebral disc degeneration since 2006; chronic urinary tract infection since 2010; left hip fracture and sepsis in 2011; and glucose tolerance impaired since 2011. The patient was also overweight (BMI 28.3 kg/m^2). Relevant concomitant medications included acetylsalicylic acid, atorvastatin, and sildenafil citrate.The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 27 days from (b) (6) to (b) (6) and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/80 mg for 28 days from (b) (6) to (b) (6) and FDC 10/160 mg for 28 days from (b) (6) to (b) (6). The patient then received down-titration treatment for (b) (6) days from (b) (6) to (b) (6)

   On (b) (6) 23 days after the last dose of investigational product, the patient experienced an SAE of arthralgia (severe left hip pain), and the next day, on (b) (6) he experienced SAEs of respiratory failure (respiratory failure ventilator dependent) and septic shock. There were no relevant potentially clinically significant vital signs, clinical laboratory results, electrocardiogram results, or additional diagnoses. He was discharged on (b) (6) with principal discharge diagnoses of septic shock, infected hardware, urinary tract infection, right upper extremity superficial infiltration from the pressors, electrolyte abnormalities, renal insufficiency, ventilator-dependent respiratory failure, and right upper lobe density with cavity with 8-mm nodule. Discharge medications included levofloxacin, budesonide/formoterol fumarate dihydrate, tiotropium bromide, collagenase, acetylsalicylic acid, metoprolol, atorvastatin, and omeprazole. On (b) (6) the septic shock and ventilator-dependent respiratory failure were considered resolved without sequelae. As of 25 Jan 2013 the event severe left hip pain was continuing and was not expected to change. The septic shock resolved on (b) (6) (Day 100). The arthralgia was ongoing at the time of this report, and no resolution date was provided for the respiratory failure.

3. SAE of ankle fracture at 10/160 mg: a 54-year-old female with a 4-year history of hypertension. The patient's other relevant medical history included hyperglycemia, hyperlipidemia, and obesity since 2008 (BMI at study entry was 35.6 kg/m^2). Concomitant medications at the time of the ankle fracture included metformin. The patient participated in Study NAC-MD-01, during which she took single-blind placebo for 35 days from (b) (6) to (b) (6) and was then randomized to fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/80 mg for 29 days from (b) (6) (b) (6) to (b) (6) and 10/160 mg for 31 days from (b) (6) to (b) (6) The patient then received down-titration treatment for 4 days from (b) (6) to (b) (6).

   On (b) (6) (Study Day 33), the patient experienced an SAE of ankle fracture (fracture of right ankle). At the time of the ankle fracture, the patient was taking FDC 10/160 mg. There were no relevant potentially clinically significant vital signs, clinical laboratory results, electrocardiogram results, or additional diagnoses. The patient sustained a fracture of the right ankle, as a result of slip and fall, while taking out the garbage at night. The patient was hospitalized, and the next day, on (b) (6) (b) (6), she underwent surgical repair and was placed in a cast. She was discharged to her home on (b) (6) Discharge medications included oxycodone/acetaminophen, cephalexin, and enoxaparin. The patient reported that she did not take the investigational product for 3 days from (b) (6)

through 22 Nov 2012; she restarted on 23 Nov 2012. There was no reported treatment for the ankle fracture, which was ongoing at the time of this report.

4. SAE of calculus ureteric at 10/160mg: A 55-year-old male with a 3-year history of hypertension. The patient's other relevant medical history included hyperlipidemia since 1997, hypothyroidism since 2002, and obesity since 2004 (BMI was 43.5 kg/m^2 at study entry). No concomitant medications were reported in the study database. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 35 days from 29 May 2012 to 02 Jul 2012 and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/80 mg for 28 days from 03 Jul 2012 to 30 Jul 2012. The patient was discontinued from the study because of insufficient therapeutic response, and he received down-titration treatment with FDC for 7 days from 31 Jul 2012 to 06 Aug 2012.

   The double-blind investigational product was discontinued on 06 Aug 2012. The patient experienced abdominal pain beginning on 28 Aug 2012, and he was evaluated in a doctor's office the following day. An ultrasound of the gallbladder was recommended. On (b) (6), the patient went to the emergency room because of increased abdominal pain and was admitted. Computerized tomography scan of the abdomen showed an obstructive calculus of the right ureter. A Foley catheter was inserted. On (b) (6), he underwent a cystoscopy and right double-J stent insertion. He tolerated the procedure well without complications, and his Foley was removed the following day. Treatment medication included hydromorphone, ondansetron, ketorolac tromethamine, levofloxacin, tamsulosin, ciprofloxacin, docusate, and acetaminophen/oxycodone. On (b) (6), the ureteral calculus was considered resolved without sequelae, and the patient was discharged. The patient was instructed to follow up with his urologist for a right ureteroscopy for stone removal. The calculus ureteric resolved on (b) (6).

5. SAE of acute myocardial infarction associated with premature study discontinuation at dose of 10/320 mg: A 52-year-old female with a 2-year history of hypertension. The patient's other relevant medical history included hyperlipidemia and type 2 diabetes mellitus since March 2010 and obesity since March 2012 (BMI at study entry was 41.3 kg/m^2). Relevant concomitant medications included glibenclamide, lovastatin, and metformin. The patient participated in Study NAC-MD-01, during which she took single-blind placebo for 28 days from (b) (4) to (b) (4) and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/160 mg for 25 days from (b) (4) to (b) (4) The patient did not undergo down-titration.

   On (b) (4) (Study Day 26), the patient experienced an SAE of acute myocardial infarction (non-ST myocardial infarction). At the time of the acute myocardial infarction, the patient was taking FDC 5/160 mg. The patient was hospitalized on (b) (4) for an acute myocardial infarction. The patient complained of chest pain that was localized midsternal/left chest and had elevated troponins (5.9, units and reference range not provided). She was treated with enoxaparin, eptifibatide, and metoprolol. On (b) (4) coronary angiography showed coronary artery disease; the left circumflex distal artery was totally occluded, the left circumflex was very small, the left anterior descending artery had mild diffuse irregularities, and the ejection fraction was 60%. Further treatment included a beta-blocker, a statin, acetylsalicylic acid, an angiotensin-converting enzyme inhibitor, and treatment for her diabetes. On (b) (4) the patient was discharged, and the event was considered resolved without sequelae. The patient was discontinued from the study because of the acute myocardial infarction, which resolved on (b) (4) (Study Day 28).

6. SAEs of atrial fibrillation and supraventricular tachycardia: A 47-year-old male with a 13-year history of hypertension. The patient's other relevant medical history included palpitations since 1978, and, per MedWatch, alcoholism since 1985. The patient was also obese (BMI 36.3 kg/m^2). Relevant concomitant medications included acetylsalicylic acid. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 28 days from (b) (6) to (b) (6) and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/160 mg for 29 days from (b) (6) to (b) (6) and FDC 10/320 mg for 27 days from (b) (6) to (b) (6). The patient then received down-titration treatment with FDC for 7 days from (b) (6) to (b) (6).

   On (b) (6), the patient reported feeling his heart fluttering and was admitted to the hospital. Electrocardiogram results showed atrial fibrillation with left anterior fascicular block and supraventricular tachycardia with wide complex beats. A transthoracic echocardiogram revealed normal left ventricular chamber size, moderate concentric left ventricular hypertrophy, estimated left ventricular ejection fraction of 60% to 85%, abnormal left ventricular diastolic filling consistent with impaired left ventricular relaxation, left ventricular filling pressures in the normal range, mild mitral regurgitation, mild tricuspid regurgitation, right ventricular systolic pressure estimated at 28 mm Hg, and no pericardial effusion. On (b) (6), the patient underwent an ablation procedure and recovered from the event. There was no reported treatment for the atrial fibrillation and supraventricular tachycardia. Both events resolved on (b) (6) (Study Day 69).

7. SAEs of fall and pneumothorax at 10/320 mg: A 62-year-old male with a 30-year history of hypertension. The patient's other relevant medical history included hypercholesterolemia since 2000 and cardiac murmur since 2010. The patient was also obese (BMI 37.0 kg/m2). Concomitant medication at the time of the fall and pneumothorax included simvastatin. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 34 days from (b) (6) to (b) (6) and was then randomized to fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/160 mg for 29 days from (b) (6) to (b) (6) and 10/320 mg for 27 days from (b) (6) to (b) (6). The patient then received down-titration treatment with FDC for 7 days from (b) (6) to (b) (6).

   On (b) (6) (Study Day –31), during the placebo run-in, the patient experienced SAEs of fall (mechanical fall) and pneumothorax (right anterior pneumothorax) and nonserious adverse events of laceration (right elbow laceration), rib fracture (nondisplaced fracture right 4th and 5th ribs), and traumatic lung injury (minimal pulmonary contusion). At the time of the events, the patient was taking single-blind placebo. There were no relevant potentially clinically significant vital signs, clinical laboratory results, electrocardiogram results, or additional diagnoses.

8. SAE of appendicitis at 10/320 mg: A 44-year-old male with a 24-year history of hypertension. The patient had no additional relevant medical history and was not taking any relevant concomitant medications. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 42 days from (b) (6) to and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 5/160 mg for 29 days from (b) (6) to (b) (6) and FDC 10/320 mg for 26 days from (b) (6) to (b) (6). The patient then received down-titration treatment with FDC for 7 days from (b) (6) to (b) (6) (b) (6)

   On (b) (6) (Study Day 46), the patient experienced an SAE of appendicitis. At the time of the appendicitis, the patient was taking FDC 10/320 mg. There were no relevant potentially clinically

significant vital signs, clinical laboratory results, electrocardiogram results, or additional diagnoses. On (b) (6), the patient experienced symptoms of appendicitis and was hospitalized. CT scan and physical examination findings were consistent with appendicitis, and the patient underwent a laparoscopic appendectomy. The patient was discharged on (b) (6). Investigational product was not interrupted. The patient was treated with ciprofloxacin (750 mg) and oxycodone/acetaminophen (5/325 mg). The appendicitis resolved on (b) (6) (Study Day 47).

9. SAE of diverticulitis at 20/320 mg: A 46-year-old male with a 9-year history of hypertension. The patient's other relevant medical history included type 2 diabetes mellitus since May 2006 and gastroesophageal reflux disease and hepatic steatosis since June 2008. The patient was also obese (BMI 41.3 kg/m^2). The patient was not taking any concomitant medications relevant to the SAE. The patient participated in Study NAC-MD-01, during which he took single-blind placebo for 29 days from (b) (6) to (b) (6) and was then randomized to double-blind fixed-dose combination (FDC) of nebivolol and valsartan. The patient received FDC 10/160 mg for 30 days from (b) (6) to (b) (6) and FDC 20/320 mg for 27 days from (b) (6) to (b) (6). The patient then received down-titration treatment with FDC for 7 days from (b) (6) to (b) (6)

   On (b) (6) (Study Day 14), the patient presented to the emergency room with significant abdominal pain. A computerized tomography scan of the abdomen and pelvis showed findings compatible with acute diverticulitis involving the mid-sigmoid colon with significant stranding formation with extension into the distal descending colon. On (b) (6), the patient recovered from the diverticulitis and was discharged. No action was taken against the investigational product.

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/s/

SHEN XIAO
08/06/2014

ALIZA M THOMPSON
08/07/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206-302 **Applicant:** Forest Laboratories Inc. **Stamp Date:** February 26, 2014

Drug Name: (b) (4) (Nebivolol/valsartan) **NDA/BLA Type:** NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		The Division agreed the Summary of Clinical Safety would suffice
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		The Division agreed the Summary of Clinical Efficacy would suffice
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(2)			The reference drugs are appropriate (nebivolol/valsartan)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application? Pivotal Study #1 Indication: Hypertension				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	The pivotal trial was conducted in the US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	The pivotal trial was conducted in the US
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Shen Xiao	4/1/2014
Reviewing Medical Officer	Date
Aliza Thompson	4/7/2014
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEN XIAO
04/08/2014

ALIZA M THOMPSON
04/08/2014